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Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin

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Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin

Proceedings

of a

Symposium

held in

Kona, Hawaii

January 16–20, 1984

Sponsored by:

Special Programs Branch
Division of Cancer Etiology
National Cancer Institute

Chairman:

Brian E. Henderson, M.D.

INTRODUCTION

The Fourth Symposium on Cancer Epidemiology and Registries in the Pacific Basin was held at Kona, Hawaii, January 16–20, 1984. A total of 82 participants from 13 countries made this the largest in this series of symposia. By general consensus, this Symposium was the most successful so far, both in technical and scientific quality of the presentation and the substantial evidence that collaborative research activities in the Pacific Basin were yielding significant results.

An important part of the success was due to the presence of a large delegation of 11 epidemiologists and clinicians from the People's Republic of China. With funds provided by the National Cancer Institute, a two-day symposium on U.S.–China Cooperative Epidemiological Research was held immediately prior to the regular meeting. It is particularly satisfying to me to see such remarkable evidence of collaborative research. When I first visited China in 1977, the Cancer Atlas was just being prepared and already provided the promise of exciting prospects for etiologic research. I subsequently returned to China for 3 months in 1982 and had the opportunity to visit many of the high-risk cancer areas. I happened to be in Beijing when Dr. William Blot arrived and was able to join him during the initial planning of the case–control studies of cancers of the lung, esophagus, and stomach and choriocarcinoma now sponsored by the National Cancer Institute. Although some may have doubted the feasibility of such collaborative studies, the record now speaks clearly and with confidence that the results will be of great importance not just to China and the United States but to the entire world.

The formal sessions of the Symposium included the first presentations of the results of important research that have come from the collaborative atmosphere in the Pacific, several of them direct results of this series of symposia. Among the most interesting of these presentations were the 1) substantial evidence that Cantonese salted fish is a cause of nasopharyngeal carcinoma, 2) excess of lung cancer in Chinese women is not explained by cigarette smoking, 3) lack of evidence supporting the role of dietary fat as a cause of colon cancer in Japanese in Hawaii, 4) investigation of the role of N-nitroso compounds and salt consumption as risk factors for stomach cancer in Colombia, and 5) careful elucidation of the role of hepatitis B virus and other factors as causes of liver cancer in Shanghai.

In addition, several presentations were given on the possible role of vitamin A, β-carotene, and other micronutrients on the risk of epithelial cancers. The ingestion of vegetable sources of vitamin A seemed to be protective against a broad range of epithelial cancers in data from Japan and protective against lung cancer in Hawaii. The rationale and design of clinical trials of micronutrients and protection from lung cancer in Seattle and esophageal cancer in Linxian, China, are also described.

Four workshops were conducted concurrently during 2 afternoon sessions covering the subjects of 1) hormones, 2) diet, and 3) other life-style factors (e.g., smoking, betel nut, and analgesics) as causes of cancers, and 4) methodologic issues on cancer registration. These workshops were highly successful, and summaries of them are included at the end of this monograph.

In summary, this was indeed a successful Symposium, and we look forward to the future of epidemiologic cancer research in the Pacific Basin.

Brian E. Henderson, M.D.

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SESSION I

United States–People's Republic of China Cooperation in Cancer Research

Recent History of China–United States Cooperation in Cancer Research [1, 2]

You-Hui Zhang [3]

It may not be superfluous for us to recall the early history of the development of collaborative research on cancer epidemiology between China and the U.S. After President Nixon's visit to the People's Republic of China in 1972, diplomatic relationships between our 2 nations were restored. Since then, the impetus of scientific exchange has grown steadily. In 1977, the Cancer Delegation led by Dr. Henry Kaplan and Dr. William Terry was the twenty-first such scientific delegation to China under the auspices of the CSCPRC. Among members of the delegation were Dr. Robert W. Miller, Dr. Bernard Weinstein, and Dr. Brian E. Henderson. The visit was a success. One of the reasons for the success, as Dr. Kaplan pointed out in (*1*), "undoubtedly was that the interests of the delegation members matched those of the Chinese cancer scientists." Dr. Miller told us more than once that he found that epidemiologists of our 2 countries were doing similar cancer epidemiologic surveys independently without knowing of each others' work. The results of the surveys revealed important differences in cancer status of the 2 countries. For instance, China and the U.S. have entirely different cancer patterns; many commonly seen in China are rare in the U.S. and vice versa. However, like the U.S., several types of cancer seen in China show characteristic geographic distributions with well-defined, high-risk areas. In 1980, Dr. Bing Li, Dr. Min Xin Li, and I were invited by the CSCPRC to return the visit. The Chinese Cancer Atlas became available at that time. The results of the national cancer survey in China and the colored maps were introduced to many more American colleagues with whom we met. What impressed us most was that the epidemiologists from our 2 countries had many common interests. Moreover, I can still remember Dr. Miller pointing out that, for each type of cancer, at least 20 papers could be prepared from the results of the nationwide survey in China. To me, it means that new ideas so developed will yield many more epidemiologic research programs. While Dr. Jun-Yao Li was at the National Cancer Institute in Bethesda, Maryland, in 1981, Dr. Fraumeni, Dr. Blot, and many others were deliberating the possible areas of meaningful collaboration which became the embryonic form of the ongoing case–control studies and the nutritional intervention study described later in this monograph. Dr. Henderson visited China again in 1982 under the Distinguished Scholar Exchange Program sponsored by the CSCPRC and the Chinese Association of Science and Technology. He had wide contact with Chinese colleagues and, as a result, joint research projects on nasopharyngeal carcinoma and liver and breast cancers began.

Now the China–U.S. partnership in cancer research on an institute-to-institute basis has become increasingly close and is based on mutual interest and benefit. What we have achieved is only the top of an iceberg. Inasmuch as my colleagues will present the recent progress of our collaborative research programs, I need say no more about them. As you all know, epidemiology is not my specialty. I know nothing more than the "ABCs" of cancer epidemiology, but I would like to take this opportunity to tell you, from a layman's point of view, what I expect from cancer epidemiologic studies.

Cancer is the result of an interaction between carcinogens and the host. Their relative importance depends at least partly on the magnitude of exposure to carcinogens. When constantly exposed to high concentrations of carcinogens, host factors seem to be less important. This is perhaps true of most occupational cancers among those who have been exposed to high cumulative doses of carcinogens. However, for most human cancers commonly seen (nonoccupational), host susceptibility seems to play a major role. For instance, in the high-incidence area for EC, although nitrosamines have been found in the environment, their concentrations are generally at a part-per-billion level. For years, people have been under common exposure to carcinogens; only a small proportion (0.1–0.2%) of them develop cancer each year. Therefore, it is highly significant that we know what host factors make this small proportion of people highly susceptible to environmental carcinogens. Studies in humans and animals clearly indicate that various host factors, acquired or genetic, can alter individual responses to carcinogens. Among the acquired factors, nutritional status of the host has received the greatest attention. Deficiencies in vitamins and trace elements have been shown to make the host, in one way or another, more vulnerable to carcinogens. Studies in Linxian, an EC-prone county, have revealed low serum levels of retinol, riboflavin, molybdenum, zinc, etc. These results provided a rational basis for investigators to conduct nutritional intervention trials there. Undoubtedly, this is a uniquely feasible,

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ABBREVIATIONS: CSCPRC = Committee on Scholarly Communication with the People's Republic of China; EC = esophageal cancer.

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[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

[2] Supported in part by Public Health Service grant CA34958 from the National Cancer Institute.

[3] Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

[4] *Address reprint requests to* Brian E. Henderson, M.D., Department of Preventive Medicine, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033.

prophylactic approach when thorough understanding of the carcinogens responsible for EC is still limited. Nevertheless, we must envisage that, with the pursuit of a new policy in agricultural production in China, improvement of the general nutritional condition will inevitably make the beneficial effects of vitamin and mineral supplementation over placebos less striking. Moreover, supplementing doses of vitamins may or may not be sufficient to interrupt carcinogenesis. Experiments on animals indicate that pharmacologic doses of vitamin A are required to inhibit tumor induction by chemical carcinogens. Unfortunately, toxicity has precluded its use in high doses. A number of retinoic acid derivatives with low toxicity have been developed in China that can be considered as candidate agents for chemoprevention, especially in those high-risk individuals with precancerous lesions.

That the response to environmental agents is under genetic control has been widely accepted. Ecogenetics is a new branch of genetics in which the interaction between environmental and genetic factors is studied. For instance, ample evidence has indicated that people differ in their responses to drugs. The species and individual variations in response to carcinogens are also genetically determined. A defect in DNA repair that is seen in patients with xeroderma pigmentosum is a typical example. My colleagues have demonstrated DNA repair defects in apparently healthy individuals from families prone to EC. With powerful genetic engineering technology, we may be able to correct these defects in the foreseeable future. The mere identification of the genetic susceptibility to a carcinogenic effect can at least help pinpoint high-risk individuals who require close surveillance and active chemoprevention.

To stress the major role of host factors modifying the carcinogenic process does not mean that we should ignore the importance of environmental carcinogens. Whenever possible, prophylactic measures should be directed to both because they are complementary. Epidemiology is a powerful weapon with which we can test and verify etiologic hypotheses. The only possible way we can ascertain human cancer etiologic agents is to conduct precise, quantitative, prospective epidemiologic studies correlating the magnitude of exposure to carcinogens and cancer occurrence. The magnitude of exposure cannot be judged simply by the concentrations of a particular carcinogenic substance in the immediate environment to which an individual is exposed. It must be determined by measurement of the amount of the substance that has actually entered the body. Precise information can be obtained by direct measurement of the concentration of either the parent compound or its metabolites in body fluid and excreta. Using the techniques of radioimmunoassay and high-performance liquid chromatography, my colleagues have quantitated aflatoxins in the urine of persons living in an area known for its high incidence of liver cancer. From these results, we not only know the magnitude of exposure to aflatoxins on an individual basis but also can pinpoint the source of mycotoxin contamination. Measurement of carcinogens and their metabolites in the body fluids is even more important when nitrosamines are suspected to be the causative agents because they can be preformed in the environment or synthesized de novo from precursors in vivo. So far, we have demonstrated a number of nitrosamines in the environment of Linxian but none in human body fluids. However, nitrosarcosine, a nitrosamine which selectively induces EC in rats, has recently been found in Linxian in human body fluids in amounts threefold higher than those in Fanxian, where the incidence of EC is low. Another nitroso compound, *N*-nitrosothiozolidine 4-carboxylic acid is also present in the urine in much higher concentrations than is nitrosarcosine, but its significance has not been determined. These substances have not been detected in the local environment and apparently are synthesized in the body. In fact, in vivo nitrosation in man has been demonstrated by the urinary excretion of nitrosoproline after ingestion of a standard dose of L-proline (100 mg, three times/day).

We all know that many carcinogens are precarcinogens in the sense that they must be enzymatically activated before they can bind to macromolecules, such as DNA, which are directly involved in the carcinogenic process. Thus the mere measurement of carcinogens or their metabolites, or both, in body fluids may not actually indicate the real hazards that may have been produced. A more sophisticated approach is for one to detect carcinogen–DNA adducts, the formation of which is supposed to be a critical event in carcinogenesis. Because carcinogens can interact with cellular DNA only after they have been activated to electrophilic compounds, the formation of carcinogen–DNA adducts reflects metabolic activation as well. Extremely low levels of these adducts can now be detected by sensitive immunologic assays (radioimmunoassay and enzyme-linked immunosorbent assay) that require use of monoclonal antibodies. These adducts can be detected in vitro in cells and tissue that have been exposed to carcinogens. They can also be detected and quantitated in urine samples after they have been excised by endonucleases from cellular DNA.

What I am trying to say is that nutritional intervention, though feasible and most promising, must not divert our attention from the identification of cancer-causing agents that needs the joint efforts and close cooperation of epidemiologists, etiologists, molecular biologists, and immunologists.

REFERENCE

(*1*) KAPLAN HS, TSUCHITANI PS: Cancer in China. New York: Alan R. Liss, 1978

A Case–Control Study of Esophageal Cancer in Linxian, People's Republic of China [1, 2]

Jun-Yao Li, [3] Zhi-Jian Chen, [3] Abby G. Ershow, [4] *and* William J. Blot [4, 5]

ABSTRACT—A case-control study involving interviews with 1,200 patients with esophageal cancer and 1,200 population-based controls has been initiated in Linxian, a county in North Central China with perhaps the world's highest mortality rates for this tumor. Here we describe the rationale, study methods, and results of a pilot study that established the feasibility of the investigation. —Natl Cancer Inst Monogr 69: 5–7, 1985.

Annual rates of mortality from EC exceed $100/10^5$ among both males and females in certain parts of China, particularly along the eastern edge of the Taiheng mountains where Lin County (Linxian) is located (*1*). Reasons for the exceptionally high mortality, equal to or surpassing the highest in the world for this cancer, are unknown. Previous studies in Linxian and other high-risk areas of China have suggested possible risk factors, but evidence that clearly implicates any particular exposures responsible for the elevated risks is still insufficient.

Investigators initiated a case–control study in Linxian to provide further information on suspected etiologic factors. Here we describe the methods used in this study and present the results from a pilot study which established its feasibility.

BACKGROUND

The nationwide survey of mortality in 1973–75 conducted by the Cancer Institute of the Chinese Academy of Medical Sciences identified EC as the second leading cause of death from cancer in China, accounting for 27% of all cancer deaths in men and 20% in women (*1*). The survey showed remarkable geographic variation across the country, with a 670-fold gradient between counties with the highest and lowest age-adjusted rates. Although elevated mortality occurred in several parts of the country, the most prominent cluster was seen in North Central China, particularly in the Taiheng mountain area on the border of Henan, Hebei, and Shanxi Provinces. Linxian is a county in Henan Province with a population of 800,000; the crude rates per 10^5 were 135 in males and 103 in females during 1977–81, and cumulative death rates of persons to age 75 exceeded 20% in both sexes (Esophageal Cancer Institute of Lin County: Unpublished results). Although historical data are limited, it appears that EC has long been a problem in these areas and only minor changes have occurred in the age-adjusted death rates from 1959 to 1981.

In previous epidemiologic studies of this neoplasm in China, numerous laboratory investigations were conducted in areas at high and low risk [*see* (*2–9*) for summaries and original data]. In several correlation studies, levels of environmental factors (e.g., trace elements in water, food, sera, urine, and hair; nitrates in well water; consumption of pickled vegetables, moldy breads, and other foods; micronutrient levels in blood) found in residents of brigades, communes, or counties were examined in relation to the EC rates for these geographic units (*2–4*). Case–control studies were conducted in Xinjiang and Jiangsu Provinces (*2*). However, the most intense study has been conducted in Linxian, where the characteristics of EC and its precursor lesions have been under study for the past 25 years.

The studies to date have provided a series of clues to etiology, but no conclusive associations account for the geographic clusters of this cancer. In general, the high-risk areas have tended to be rural and poor with infertile soils; water is often in short supply (*2*). Until recently, diets have been typically low in fruits, vegetables, and animal foods, with deficiencies of several micronutrients, riboflavin in particular (*5, 6*). There is also evidence that some specific foods commonly eaten in Linxian and other areas may be involved. Risk factors include: pickled vegetables [by use of the Ames test, mutagenicity was identified in samples of the pickled vegetables (*3, 8, 9*)] and other foods that also become fermented or moldy, including moldy breads and cheeses in Xinjiang (*2–4*); silica fragments, most likely from ingested millet, found in esophageal tissue taken from cancer patients (*7*); and nitrosamines detected in several foods in high-risk areas.

One small experimental study also showed that cancers of the esophagus and forestomach developed in rats fed moldy cornbread, whereas another study showed that fungal contamination could promote the synthesis of nitrosamines.

ABBREVIATION: EC=esophageal cancer.

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[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

[2] Supported in part by Public Health Service contract N01-CP21012 with the Division of Cancer Etiology, National Cancer Institute.

[3] Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

[4] Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Public Health Service, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland. *Address reprint requests to* William J. Blot, Ph.D., Biostatistics Branch, National Cancer Institute, Landow Building, Room 3C16, Bethesda, Maryland 20892.

[5] We thank Doctors Ping Li, You-Hui Zhang, Guang-Yi Li, Su-Fong Zheng, C. S. Yang, Joseph F. Fraumeni, Jr., Robert N. Hoover, Brian E. Henderson, and Frederick Li for their advice, guidance, and support of this investigation.

Esophageal fungal infections were diagnosed in most patients with EC in 1 survey in Linxian (*2*). Previous studies also indicated that smoking and drinking, the major determinants of EC in Western societies, may play some role in China, but only a minor one. Familial clustering has been observed in high-rate areas, but environmental factors are probably responsible to some extent.

With this background, the case–control study was begun in 1984 after completion of the pilot study in 1983.

MATERIALS AND METHODS

Identification of patients and controls.—Diagnoses of EC occurring among all residents of Linxian aged 35–64 years over a 24-month period (1984–85) will be identified from all hospitals in the county. A reporting system (the Linxian Cancer Registry) is now in place to aid in the ascertainment of cases. A review of diagnostic material for all cancer patients will be made by an independent panel of pathologists. All cases will be included in the study, but those histologically confirmed will be treated separately from the nonhistologically confirmed in the analyses.

Controls will be randomly selected from all individuals in the Linxian population of similar age and sex but without EC. We developed the following scheme for the sampling of individuals. To obtain a control in a specific sex and age category (e.g., a female 50–54 yr old), we randomly select (using a random number table) a commune from among the 15 in Linxian, weighting according to the numbers of women of the same age. These populations are known from a recent census of Linxian. Next a brigade[6] is randomly chosen, again weighting the brigade's chances according to the populations in the sex–age group for that brigade. We then visit the brigade office and randomly select a team, weighting according to its total population (the age distributions of the teams are not readily known but are generally similar within brigades). Each brigade office maintains a book listing all residents of each team. We then read the book for the team selected to find all women 50–54 years old, 1 of whom is randomly selected as the control. This process is repeated for each control.

Data to be collected.—Patients and controls will be interviewed by trained interviewers using a structured questionnaire. Data obtained from the interview form the primary outcome measures to be examined in this case–control study. The questionnaire includes sections on detailed histories of residence, occupation, smoking, diet, food preparation and storage, beverage (e.g., alcohol, tea) consumption, anthropometry, medical conditions, and other factors. In addition, blood and urine specimens will be collected from a sample of patients, spouses and controls. The blood will be analyzed for serum retinol, carotene, vitamin E, and other indexes of nutritional status;

Sample size.—At present rates, about 1,200 EC would be diagnosed in Linxian among adults aged 35–64 years over a 24-month period. The study will include all 1,200 plus 1,200 frequency-matched population controls. This will enable the detection of increased relative risks of 1.5 or higher with reasonably high power for all the variables of primary interest [specifically, for any variable reported in about 10 to 90% of the controls, the study could detect increased relative risks of 1.5 or greater with power exceeding 95% (one-sided alpha = 0.05); the power still exceeds 80% for exposures occurring in as few as 5% of the controls]. The large size of the study will enable the evaluation of interactions between variables.

Interviews.—Structured interviews will be conducted by trained interviewers using a questionnaire developed in the pilot study. All interviews will be with the patients and controls individually.

Quality control procedures.—The following procedures were established in the pilot study for maintenance of quality control: 1) A written log was kept of all decisions that affected study design, conduct, or analysis. 2) Interviewers were provided with instructions that are easily understood. 3) Field workers attended a training course for 2 weeks before the survey, so that their capability was ascertained. 4) Reinterviews of 10% of all subjects were conducted, and 10% of all records were reabstracted. 5) Field workers listed all the problems encountered in field work and informed the field supervisor about them. 6) All the completed questionnaires and medical abstracts were edited by the field supervisor or his assistant. 7) Coding of data was checked for accuracy.

Data processing and analysis.—After checking all abstract and interview information, coding sheets will be prepared for data computerization at the National Cancer Institute, Bethesda, Maryland. Statistical analysis of the collected data will utilize standard epidemiologic techniques as described for case–control studies (*10*).

PILOT STUDY RESULTS

A pilot study was conducted in 1983 for the establishment of procedures rather than provision of data for etiologic analyses of differences for this case–control study of EC in Linxian. A rapid case-reporting system was developed based on the existing system of cancer registering in Linxian. Patients with EC were identified through weekly visits to each of the 15 commune hospitals in the county and a daily visit to the county hospital. For the pilot study, all incident cases during a month were to be ascertained. From April 16 to May 15, 1983, we identified 112 cases reported from the commune and county hospitals. Of these, 28 patients were outside the 25- to 64-year age range, 3 were not Linxian residents, 13 were prevalent but not incident cases, 4 were judged by our review panel (a clinician, pathologist, and cytologist from the Cancer Institute and Henan Medical College) not to have EC. Thus the remaining 64 were eligible. The utility of this system as a mechanism for rapid identification was found satisfactory because the average time from diagnosis to interview was 8.6 days. Sixty-five controls were selected according to the procedure described above.

A questionnaire for the pilot study based on suggestions made by attendees at a workshop held in Beijing and Linxian in October 1982 was developed. A copy of it

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[6] Each commune is divided into brigades (493 in the county), and each brigade is divided into teams (about 4,000 in the county) whose populations average about 200 persons.

TABLE 1.—*Demographic characteristics of the Linxian pilot study sample*

Indicator	Percent
Sex	
Male	55
Female	45
Birthplace	
Linxian	94
Other	6
Education	
None	62
1-5 yr	33
5+ yr	6
Debt to Government in 1970s	
Owed	31
Received	48
Even	21
Debt to Government in 1950s	
Owed	58
Received	13
Even	29
Had 5 or more children	
No	24
Yes	76

TABLE 2.—*Distribution of responses to selected questions from the Linxian pilot study*

Indicator	Percent
Ever smoked cigarettes[a]	41
Ever drank alcoholic beverages	24
Had a family member with cancer	37
Ever worked 1+ years in nonfarming job	37
Usually brush teeth	34
Ate wheat flour in 1950s	12
" " " " 1970s	13
Ate corn daily in 1950s	39
" " " " 1970s	60
Ate spinach daily in season in 1950s	35
" " " " " " 1970s	39
Pickled vegetable consumption in 1950s	
None	42
<Daily	13
Once/day	23
>Once/day	22
Pickled vegetable consumption in 1970s	
None	38
<Daily	17
Once/day	25
>Once/day	19

[a] Median number of cigarettes smoked/day was 7.5; median age at which subjects started to smoke was 25 yr.

(Chinese or English versions), which incorporates revisions suggested by results of the pilot study, is available upon request. The amount of time an interviewer spent in completing the questionnaire ranged from 63 to 89 minutes.

Of 64 patients with EC, 2 could not be located in the allotted time (these persons were registered as Linxian residents but may have come to Linxian from neighboring areas); all but 1 of the remaining 62 were interviewed. All 65 controls were interviewed, so that the overall participation rate was 116 of 119 or 97%.

Table 1 shows demographic characteristics of the pilot study sample, and table 2 presents distributions (for patients and controls combined) for selected variables asked about in the interview. Considerable variation occurred for many exposure variables within Linxian, even for some dietary items, thus dispelling the notion that such exposures may be uniform throughout the County. This suggests that the findings of the full-scale case-control study should be adequate to quantify risk among several categories of each variable of interest.

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A Case–Control Study of Stomach Cancer in Shandong Province [1, 2]

Tian-Gen Wang, [3] Wei-Cheng You, [3] Brian E. Henderson, [4] *and* William J. Blot [5]

ABSTRACT—Stomach cancer is the leading cause of death from cancer in China. Although the causes of this cancer are unknown, special opportunities exist for the evaluation of etiologic factors in Linqu County in Shandong Province where rates are exceptionally high. We have described here a newly initiated case–control study, which focuses on certain dietary items as risk factors for stomach cancer in Linqu.—Natl Cancer Inst Monogr 69: 9–10, 1985.

During a nationwide retrospective survey of cancer mortality, data on the causes of death were collected over a 3-year period (1973–75) from the Chinese population of over 800 million persons (*1*). An unexpected result was that stomach cancer ranked first for males and females in cancer mortality. The crude mortality rate for gastric cancer was 17.3/100,000 population per year (160,694 deaths in 1975), and the age-adjusted rate (with the Chinese population in 1964 as the standard) was 15.4. A comparison with the mortality rates for gastric cancer in 23 other countries revealed that the overall rate in China is lower only than the rates reported in Japan, Chile, Costa Rica, and Hungary (*2*).

Since that time, a national epidemiologic and etiologic comprehensive survey of stomach cancer was conducted in the countryside of China, involving 12 counties in 9 provinces (*3*). The main parts of the survey were: correlation studies, case–control studies with a total number of 700 cases, determination of nitrate and nitrite in gastric juice and environmental items (specimens from water, grains, and vegetables), determination of fungi in gastric juice, and the prevalence of different types of gastritis. Several clues were generated from this project, including inverse associations between mortality and the consumption of fresh vegetables, high grain rations, animal protein, fat and oil, and bean products. Positive associations were seen with consumption of moldy grains, salty vegetables and salted foods, and meal irregularity (*3*). Thereafter, a coordinated case–control study of stomach cancer conducted in large cities in China (*4*) revealed high risks associated with family history of cancer and a negative association with the consumption of fresh vegetables.

These preliminary studies suggest several possible risk factors for stomach cancer in China, but in each area the number of cases studied was small (less than 100), and limited detail was available on specific food items. The interrelationships between positive risk factors (e.g., moldy grain, salty food) and protective factors (e.g., vegetables and their relative concentrations of vitamin A and ascorbic acid) could not be evaluated. Therefore, in a China–U.S. collaborative venture, we developed a detailed protocol to study gastric cancer in a high-risk rural area of China, i.e., Linqu County in the center of Weifang Prefecture in Shandong Province.

During the nationwide cancer survey, this County had one of the highest rates of stomach cancer mortality in China. The age-adjusted (China standard) rate was 55/100,000 and 19/100,000 in males and females, respectively; these rates are among the highest in the world. The County has a population of about 700,000; over 400 people die from stomach cancer each year (42% of all deaths from cancer). In early 1983, we resurveyed all mortality in Linqu County from 1979 to 1983 and found no appreciable change in the rate over 13 years.

Linqu, a mountainous region easily accessible from Weifang City, is a poor area with infertile soil and periodic severe droughts. The physicians, health workers, and government officials of Linqu County provided great support in developing this research project.

In the case–control study in Linqu County, we will attempt to identify risk factors responsible for the high rates of stomach cancer. Information on demographic and socioeconomic conditions, smoking, alcohol consumption, occupation, and medical history will be obtained, but the primary focus will be on diet. In the questionnaire, several factors will be explored in detail, including eating habits and cooking methods; the type and quantity of grain eaten; consumption of fresh vegetables and fruits, animal protein, fats, bean products, salt and salty foods, and sour pan cake, a special kind of food commonly eaten in Linqu County.

MATERIALS AND METHODS

Identification of patients and controls.—Incident cases of stomach cancer among Linqu County residents are being identified from medical records at the Linqu County and neighboring Yidu County Hospitals by the staff of the Beijing Cancer Institute in collaboration with local pathologists. For those small numbers not diagnosed at the County Hospitals, we established a reporting network to identify patients from clinics in the communes of Linqu.

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[2] Supported in part by Public Health Service contract N01-CP21012 with the Division of Cancer Etiology, National Cancer Institute.

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To increase the potential for accurate recall, we limited our selection to persons under 65 years of age; it will also be restricted to those who have been residents of Linqu for at least 10 years. We expect to register about 600 such persons over 1½ years. All must have a confirmed diagnosis of stomach cancer: Approximately 60% are expected to be histopathologically confirmed, with the remainder diagnosed on clinical and radiologic grounds. All diagnoses will be reviewed by a panel of radiologists and pathologists. About 20% of the subjects will be selected at random, and their diagnoses will be reviewed by a senior pathologist at the Beijing Institute for Cancer Research. Their medical records will be abstracted by trained abstractors, and 10% of all abstracts will be redone by their supervisors.

Controls will be randomly selected from the general population of Linqu County. They will be frequency matched to patients by sex and 5-year age group; the residency requirement is the same as that for subjects. We expect that 25–30% of the controls will have a history of chronic gastritis (manifested by bleeding or pain), so we will choose 2 controls/patient to increase the likelihood that at least 1 will not have chronic gastric disease. The 2 controls will be ascertained from the census lists maintained in each village.

Development of questionnaire.—We made several visits to Linqu County in late 1982 and early 1983 to prepare a comprehensive list of food items, cooking and preservation methods, and other habits. A questionnaire was then developed and included: 1) all food items most likely to be consumed; 2) the amount consumed according to frequency by day, week, month, year (or whatever period is most relevant to the respondents) and size of portion; 3) seasonal differences; 4) variation in consumption in recent years (prior to cancer diagnosis) from that of 15 years ago;[6] 5) special habits, such as eating sour pan cake and salted vegetables; and 6) information on nondietary variables, such as smoking history, residence, occupation, and cancer in first-degree relatives.

Urine and blood samples.—To evaluate salt ingestion, we intend to measure sodium (and creatinine) in a sample of patients and controls and their families. Twenty percent of the married subjects and their spouses and 20% of the controls will be randomly selected and asked to provide urine samples. Blood will also be drawn from these individuals and analyzed for micronutrients (e.g., serum retinol, tocopherol, and beta-carotene). Saliva will also be obtained for assay of Lewis antigens, a potential marker for gastric carcinoma (*5*).

Data analyses.—Standard methods for analyses of case–control data as described by Breslow and Day (*6*) will be followed.

FEASIBILITY OF THE PROPOSED CASE-CONTROL STUDY

From May 25 to July 21, 1983, we conducted a pilot study in Linqu County. Our objectives were to 1) recruit and train competent abstractors, interviewers, and information collectors, 2) identify gastric cancer patients and interview a high proportion before they were too sick or dead, 3) identify and interview controls, and 4) establish quality control procedures for data collection.

We used nonmedical professional people as information collectors, abstractors, and interviewers who did not know the specific aims or hypotheses of the study and trained them specifically for this study. The abstractors visited the Linqu and the Yidu County hospitals, the 13 commune clinics in Linqu, and the Prefecture Hospital in Weifang. Of the 75 prevalent cases identified, 55% had been diagnosed by histopathology and 45% by an x-ray examination. Two patients were too sick to be interviewed, but the remaining 73 provided the information requested.

The controls were randomly selected from all persons of the same sex and 5-year age group from villages where the patients lived (excluding those with the same surname). One control was selected for each patient. Lists of the appropriate controls (usually 10–15 names) were obtained from the village headquarters, and 3 controls were randomly selected and registered. Then the selected persons were sought for the interviews, which usually took place on the same day and by the same interviewer.

Inasmuch as approximately 30% of the controls gave a history of chronic stomach disease, we will select 2 controls/patient in the full-scale study. This will allow comparison of subjects with all controls and with those free of clinical stomach disease, and it will also permit a comparison of controls with and without stomach disease.

The feasibility study indicated that patients should be readily identified and controls selected. Although patients whose stomach cancer was confirmed and village controls were used in the pilot study, the methods of ascertainment can be easily adapted to select those whose disease was in the developing stage and population controls in the full-scale study. The local medical community and the villagers themselves were willing participants in the feasibility study, so that response rates can be expected to be high (95% or greater) in the full study. We hope it will provide information useful in determining reasons for the high rates of stomach cancer in Linqu and lead to preventive measures.

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[6] The beginning of the Cultural Revolution, 1966, is used as a reference date.

A Case–Control Study of Lung Cancer in Shanghai [1, 2]

Yu-Tang Gao,[3] Chong-Wen Hsu,[4] William J. Blot,[5] *and* Joseph F. Fraumeni, Jr.[6, 7]

ABSTRACT—Lung cancer mortality rates are higher in Shanghai than all other large cities in China, with rates for females among the highest in the world. In this paper, we describe a case–control study now under way in Shanghai to evaluate reasons for this pattern, reviewing what is known about the risk factors under study. The objectives and methods used in the investigation are outlined.—Natl Cancer Inst Monogr 69: 11–13, 1985.

Lung cancer ranks fourth among men and fifth among women in cancer mortality in China (*1*). Lung cancer rates are exceptionally high in some parts of the country. One such area is Shanghai, which leads all other major urban centers in China in lung cancer mortality. Data for 1976–77 from the Shanghai Cancer Registry show annual age-standardized mortality rates of 56 and 20 per 10^5 males and females, respectively (*2*). Whereas the rate for males is comparable to that among white males in the U.S. in the mid-1970s, the rate for females is nearly double that found in the U.S. The high rates in a large population result in more cases of lung cancer being diagnosed among women in Shanghai than in any other city in the world. Mortality from lung cancer in Shanghai is also on the rise, with recently reported rates approximately twice those of the early 1960s. A case–control study of lung cancer is being conducted in Shanghai for the evaluation of reasons for the high rates of this tumor and the unusual susceptibility of Chinese women.

STUDY OBJECTIVES

The case–control study will allow assessment of various hypotheses raised to explain the elevated rates of lung cancer in Shanghai compared with other parts of China and the special predisposition of Chinese women to this tumor.

Smoking

The major cause of lung cancer in Western societies is cigarette smoking (*3*). Its influence is not as conclusively established in China, but smoking seems likely to be a significant factor, particularly in men. However, a preliminary survey of female lung cancer in Shanghai by one of us (Gao Y-T) showed that about 72% of women with lung cancer are nonsmokers. Results of case–control studies in Singapore (*4*) and Hong Kong (*5*) have also revealed that a large percentage of female lung cancers occur in nonsmokers. In addition, the high rates of this neoplasm reported among Chinese women in Hawaii and San Francisco appear related to factors other than smoking (*6, 7*). The lung cancers in women are often adenocarcinomas and arise in the distal portions of the lungs. These tumors are less often related to smoking than are squamous cell carcinomas, which predominate in men and arise frequently in more central portions of the lungs. Thus one of our major goals is to clarify the lung cancer risks associated with cigarette smoking in both sexes. We will also assess secondary exposures to smoke in the home and workplace, especially among nonsmokers, to investigate possible risks from passive smoking.

Occupation

Lung cancer is a well-documented occupational disease among various groups of workers exposed to asbestos, steel workers exposed to coke oven emissions, miners to radon, and smelter workers to inorganic arsenic (*8*). Shanghai is a major manufacturing and trading center with large shipyards, steel mills, and other heavy industries. Detailed work histories will help quantify occupational risks among men and women. The large sample size of the study will also enable assessment of interactions between certain occupational exposures and smoking.

Air Pollution

Atmospheric pollution has long been suspected as a risk factor for lung cancer, but establishment of supporting evidence has been difficult for various reasons. The exposures are comparatively low, and the effects are not easily distinguished from those of smoking and occupation. In addition, problems have been encountered in the assessment of exposure to various pollutants in the past and present (*9*). Particulate emissions in Shanghai come not only from industry but also from heating and cooking sources and a small amount from automobile exhausts. In

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this study, the role of air pollutants will be evaluated by determination of whether cases are clustered in residential areas where industrial pollution levels are high and by analysis of case–control differences (particularly for women) in exposure to airborne particulates within the home. Home exposures will be estimated by information gained from types of heating facilities, equipment and methods used in cooking, practices of incense burning, ventilation, and smoking habits of family members.

Diet

Recent interest has focused on the possible protective role of beta-carotene, retinol, and other micronutrients in the diet (*10*). Several epidemiologic investigations outside China indicate that patients with epithelial cancers, including those of the lung, often have diets characterized by a reduced intake of certain foods, particularly fruits and vegetables. A case–control study of Chinese women with lung cancer in Singapore has also implicated low consumption of green vegetables as a risk factor (*4*). We will obtain data on dietary patterns to classify individuals into broad categories of consumption of various foods, food groups, and nutrient indexes. Anthropometric and other nutrition-related data will also be used.

Other Factors

We will examine the possible effect of chronic respiratory diseases, including tuberculosis (*11*). Chronic irritation or scarring of the bronchial epithelium may enhance the subsequent development of lung cancer induced by other factors such as smoking (*12*). The effect of other medical conditions and the intake of certain Western and Chinese drugs or herbal medicines will also be evaluated.

Histories of cancer in close relatives will be obtained for an examination of familial clustering. Patterns of reproduction and childbearing will be compared between female subjects and controls. Finally, socioeconomic and demographic data will be collected from all individuals.

MATERIALS AND METHODS

Identification of patients.—All males with lung cancer aged 35–64 years newly diagnosed over a 12-month period and all females aged 35–69 years over a 24-month period will be identified among residents of the Shanghai urban areas. On the basis of the data obtained from the Cancer Registry for 1980–81, we expect about 1,500 patients.

The results of a pilot study conducted in 1983 showed that a large proportion of the new cases of lung cancer in the urban area was first reported by the Shanghai Chest Hospital and the Shanghai Anti-Tuberculosis Network. In the main study, 3 part-time workers from these 2 institutions will ascertain new cases diagnosed in their facilities, and 5 full-time workers will identify cases from other medical facilities. The notification cards on lung cancer received by the Shanghai Cancer Registry also will be used in the determination of completeness of case-finding.

Confirmation of diagnoses.—Two senior pathologists and 4 senior clinicians of the Shanghai Chest Hospital and Shanghai First and Second Tuberculosis Hospitals will review all cases in accordance with established criteria for diagnosing lung cancer. Items such as the basis of diagnosis, histologic type, location affected, and treatment are included in the abstract form of the medical history.

All pathologically, cytologically, and clinically confirmed cases of primary lung cancer will be included in the study, but histologically confirmed cases will be treated separately in the analyses.

Selection of controls.—From the general population of the Shanghai urban area, 1,500 controls will be randomly chosen, stratified by age group and sex to match the distribution of the patients. The age and sex distribution of the controls are determined by the use of the known age and sex distribution of lung cancer patients reported to the Cancer Registry during the 2-year period of 1980–81. The 1,500 controls will be distributed as follows:

Age, yr	Male	Female
35–39	8	8
40–44	19	21
45–49	55	53
50–54	124	88
55–59	233	161
60–64	323	186
65–69	—	221
Total	762	738

For each control (e.g., a male 60–64 yr old), a neighborhood committee will be randomly selected from among the approximately 1,450 in urban Shanghai. Neighborhood committee populations generally range from 3,500 to 5,000. Within the neighborhood, a household group will then be randomly selected, and the names of all males aged 60–64 years collected. Among all the eligible persons, 2 will be randomly selected. If the first is absent during the period of study or refuses to be interviewed, the second will be treated as an acceptable control. This process will be repeated until all 1,500 controls are chosen. A table of random numbers will be used as a sampling instrument.

Interviews.—All subjects will be asked to provide information on residence, smoking, occupation, diet, medical histories, and other variables. The questionnaire prepared for the pilot study has been amended with minor changes and is being used in the main study. In the pilot study, the average time required to complete the questionnaire was 71 minutes for the patients and 64 minutes for the controls.

Participation rates.—The percent of selected patients and controls who are interviewed will be calculated and the reasons for nonparticipation will be recorded. Among 70 patients registered in the pilot study, we could not interview 3 because 1 died, 1 had a debilitating disease, and another had brain metastases and was in a coma, which gave us a participation rate of 96%. Among 60 controls, 5 second-eligible persons were interviewed instead of the first because 1 person was mentally ill, 1 was absent during the study period, and 3 were retired older workers who were registered as residents in the Shanghai urban area but actually had lived outside Shanghai for a long time. Nobody refused to be interviewed. The participation rate for the first-eligible controls was 92%.

Editing and quality control procedures.—All the completed questionnaires and medical abstracts will be edited by the field supervisor or assistant to ensure completeness and accuracy. Quality control procedures include: 1) Maintenance of a written log of all decisions that affect study design, conduct, and analysis; 2) use of an interview manual with instructions easily understood by interviewers; 3) attendance at a field practice for all field workers for 2 weeks before the start of the survey for ascertainment of their ability; 4) reinterviewing of about 5–10% of subjects by each interviewer and reabstracting of an equal number of all records by each abstractor; 5) listing of all problems encountered in field work and notification given to field supervisor; 6) editing of all completed questionnaires and medical abstracts by the field supervisor or assistant; and 7) checking of coded data by the assistant field supervisor.

Biochemical analyses.—Blood specimens will be collected from a sample of subjects, their spouses, and controls. Sera will be assayed for fat-soluble micronutrients (retinol, beta-carotene, vitamin E); thiocyanate analyses will serve as a biochemical marker of exposure to tobacco smoke.

Data preparation and analyses.—All information collected will be abstracted on coding sheets for keypunching and computerization. Analyses will be based on standard multivariate techniques for case-control data (*13*).

CONCLUSIONS

The data to be collected in this case-control study should enable the testing of several hypotheses about the origins of lung cancer. The Shanghai setting offers an exceptional opportunity because of its high lung cancer rates (particularly among women); large numbers available for interview; high exposure rates for factors, such as chronic respiratory disease and indoor air pollutants; minimal confounding by cigarette smoking (due to a lower prevalence of smoking); and an established cancer registry covering a structured, stable population.

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A Case–Control Study of Trophoblastic Diseases in the People's Republic of China [1,2]

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Jun-Yao Li,[5] *and* William J. Blot[4]

ABSTRACT—A case-control study is currently under way in Beijing, People's Republic of China, involving approximately 165 patients with invasive moles or choriocarcinoma, 165 with hydatidiform moles, and 330 population controls, who were matched to the patients with invasive moles or choriocarcinoma on age and interval since last pregnancy. The interviews are focused on a number of suspected risk factors, including previous pregnancy outcomes, history of hydatidiform mole, medical factors, drug usage, family history, and diet. A brief background of the study and methods as established through a previous pilot study are given.—Natl Cancer Inst Monogr 69: 15–18, 1985.

Gestational choriocarcinoma is a particularly intriguing cancer for study, inasmuch as it is a tumor that arises from the trophoblastic epithelium and thus is a naturally occurring malignant allograft (*1*). In addition, it is a tumor for which incidence rates demonstrate marked geographic diversity, ranging from approximately 1/40,000–70,000 pregnancies in Europe and North America to a high of 1/500–1,000 pregnancies in certain countries in Southeast Asia. Because of its rarity in most countries, little is known regarding its etiology. Thus a unique opportunity exists for us to define etiologic factors by studying the disease in a high-rate area, the People's Republic of China.

BACKGROUND

Well identified as a risk factor for choriocarcinoma is a history of hydatidiform mole, with approximately 40% of all patients with choriocarcinoma having a prior molar pregnancy (*2*). The reported probabilities of women with hydatidiform moles developing malignant trophoblastic disease range from 2 to 9% (*3*). Consequently, the relative risk of choriocarcinoma associated with hydatidiform mole has been estimated to be between 2 and 4,000 times that of a woman with a normal pregnancy [possibly making it one of the largest single risk factors known for any disease (*4*)].

A survey of occurrence of hydatidiform moles in the women of the People's Republic of China showed an overall incidence rate of 0.78/1,000 pregnancies (*5*), with the rates generally higher in the southern and coastal regions. However, the extent to which this variation explains the geographic diversity of choriocarcinoma is unknown. Studies elsewhere (*6, 7*) indicate that the malignant transformation rate may actually be highest in areas showing elevated rates of hydatidiform mole. Moreover, maternal age effects and other environmental influences are undoubtedly important contributors, with the highest transformation rates having been found for mothers who develop molar pregnancies at older ages (*7–9*). Additionally, evidence indicates that molar pregnancies aborted by hysterectomy or hysterotomy may be more predisposing to malignant consequences than those by curettage or vacuum aspiration (*10*). Furthermore, recent evidence reveals that the type of molar pregnancy has differential effects because most patients requiring treatment have had complete moles (*10–12*). However, the extent to which partial moles contribute to the occurrence of subsequent choriocarcinoma has yet to be resolved (*13*).

Other than a history of hydatidiform mole, the only well-recognized risk factor for choriocarcinoma is advancing maternal age (*6, 14*), although the independence of this association from maternal age effects on hydatidiform mole has to be elucidated. Several investigators (*6, 14, 15*) have shown a relationship with multiparity, yet few have been able to distinguish the correlated effects of maternal age. Researchers in Singapore (*6*) and the Philippines (*14*) have indicated that maternal age is the most contributory factor, although further investigation of this issue is needed. Additionally, there is need for evaluation of the observation that the risk of choriocarcinoma is increased among women with either a history of fetal loss (*14*) or a stillbirth (*16*). Some (*17*) have suggested that oral contraceptive use may increase the incidence of malignant trophoblastic sequelae, particularly high-estrogen oral contraceptives (*18*), although this has not been found in all series (*19*). The relationship of oral contraceptive use to choriocarcinoma in the absence of hydatidiform mole has not been well investigated, although it has been suggested as a risk factor in 1 study (*14*).

Also proposed is that the high incidence of trophoblastic disease in Southeast Asia may be attributable to poor socioeconomic standards and malnutrition, although sub-

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Abbreviation: NCI=National Cancer Institute.

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stantive data are sparse. Specific nutritional deficiencies have not been demonstrated, but choriocarcinoma has been more common among the less affluent women in Indonesia (*20*), Malaysia (*21*), and Singapore (*6*). A high risk of choriocarcinoma in the Philippines has been noted among women with a history of pulmonary tuberculosis as well as those with poor obstetrical histories (*14*), but specific nutritional deficiencies were not discussed. Of some interest for further investigation is a report showing depressed serum folate activity in patients with trophoblastic tumors (*22*).

Further confirmation is also needed for findings that choriocarcinoma is more common in patients with group A blood (*16, 21*) or in those who show serologic incompatibilities with their husbands (*16, 23*). Measurement of human lymphocyte antigens between husbands and wives, however, shows a trend for patients to be more compatible with their husbands for B locus antigens (*24*). The effect of consanguinity on the incidence of choriocarcinoma has been suggested in part because inbred communities might tolerate a higher proportion of trophoblastic growth (*25*).

As is apparent, a number of hypotheses exist to explain the geographic variation in the incidence of choriocarcinoma; few have been tested systematically. It was with this goal that a case–control study of invasive mole and choriocarcinoma was initiated in 1984 in Beijing.

MATERIALS AND METHODS

Identification of patients and controls.—Included in the study are Beijing residents diagnosed with invasive moles or choriocarcinoma over the 7-year period from January 1979 to December 1985 at the following Beijing institutions: Capital Hospital, First Hospital of Beijing Medical College, Beijing Maternity Hospital, China Red Cross Chaoyang Hospital, Friendship Hospital, People's Hospital, Third Hospital of Beijing Medical College, and Tung Ren Hospital. Because the full-scale study began in February 1984, case identification is being pursued both prospectively and retrospectively. It was anticipated that approximately 165 patients will meet eligibility criteria for the study, of whom about 125 will be identified retrospectively and 40 prospectively.

A second series of patients will consist of approximately 165 women with hydatidiform moles who are Beijing residents and who were admitted to 1 of the 8 hospitals cited above. These patients with molar pregnancies should be followed for at least 2 years without evidence of malignant change observed. The patients with hydatidiform moles will also be identified retrospectively and prospectively.

The population controls are derived for each patient with invasive mole, choriocarcinoma, or hydatidiform mole from the same place where the patients live. From within the street unit (township in rural area), a neighborhood committee (production brigade in rural area) is randomly selected. From the police office, a roster of residents of the selected neighborhood committee (production brigade) is obtained and reviewed so that a cohort of women who match each patient on exact age is identified. Additional information regarding the interval since termination of a last pregnancy is obtained for these women from neighborhood family planning clinics and work unit health records. From the completed information on the cohort, 2 controls are selected for each case, matched on police unit of residence and exact age and interval since last pregnancy (which will be allowed to differ to a maximum of 2 yr between patients and matched controls).

Data collection.—Patients and controls are interviewed by trained interviewers using a structured questionnaire. Information collected includes the following: demographic factors; history of residence, family, occupation, medical events, reproductive behavior, hydatidiform mole, infertility, inadvertent pregnancies; contraceptive use; menstrual factors; femine hygiene practices; medication usage; paternal factors; and alcohol, smoking, and diet habits.

In addition to the interview, the medical record of each eligible subject is abstracted for documentation of details regarding the initial diagnosis (place, timing, method of confirmation, stage, type of treatment) as well as comparable information from the study hospital for referred patients.

Laboratory testing is also included for the approximately 160 subjects identified during the prospective phase of the study (40 with choriocarcinoma or invasive moles, 40 with hydatidiform moles, and 80 controls). Tentative plans include laboratory tests for ABO typing, karyotyping, and folic acid status. These tests are being performed at the Capital Hospital laboratories, where these assays have been routinely conducted on several types of patients. Additionally, ABO testing and karyotyping are being done on husbands for evaluation of the effects of paternal factors.

Interviews of study subjects.—We are attempting to interview privately all eligible study subjects, either in their homes or at the health units where they work.

Quality control procedures.—We established the following procedures to maintain quality control: 1) preparation of a field manual to standardize data collection by abstractors and interviewers; 2) organization of a field training course before the start of the survey; 3) compilation of daily log books to document all unusual field experiences, including reasons for nonresponse; 4) repetition of abstracts and interviews of a 10% sample by a supervisor to validate them; 5) editing of completed abstracts and questionnaires by the field supervisor; 6) checking of all work to ensure that coding of the data is accurate.

Data processing and analyses.—Data from abstracts, questionnaires, and laboratory tests will be entered onto coding forms and submitted at 6-month intervals to NCI for computerization. The original forms will be kept in Beijing but will be available for resolving questions arising from computer edits done in Bethesda. Statistical analyses of the collected data will be done with the use of standard epidemiologic techniques for analysis of case–control data (*26*).

PILOT STUDY

A pilot study was initiated following a 3-day workshop held in Beijing in October 1982. During this meeting, which involved staff of the Capital Hospital and the Cancer

Institutes of the Chinese Academy of Sciences and the U.S., an extensive standardized questionnaire was developed in English and later translated into Chinese. After a training session based on manuals previously used in NCI studies, 3 female interviewers were employed to identify and interview appropriate patients and controls.

Eligible for the pilot study were patients diagnosed with invasive mole or choriocarcinoma during 1978 at 5 Beijing hospitals: Capital Hospital, First Hospital of Beijing Medical College, Beijing Maternity Hospital, China Red Cross Chaoyang Hospital, and Friendship Hospital. Through an intensive review of records, 27 eligible subjects were identified for study; 1 was eventually eliminated because of a suspicious diagnosis and 1 resided outside of Beijing.

To test mechanisms for accumulating controls, we used 2 series: hospital and population controls. The hospital controls were derived from the same hospital where the patients with malignant trophoblastic disease were diagnosed. The hospital controls were individuals matched to each patient on age (± 2 yr) and time of termination of last pregnancy (± 1 mo). For the older patients ($\geq$45 yr old), the criteria were relaxed to 5 years of age and 6 months for the interval since the last pregnancy. A total of 25 hospital controls were selected in the above manner. The population controls were derived from the same places where the patients lived. First of all, the street units where the patients resided were contacted. From within the street unit, a neighborhood committee was randomly selected. From the respective police unit, a roster of residents was obtained. Two female subjects of comparable age as the patient (± 2 yr) who had been pregnant at least once were randomly selected, i.e., for the 25 patients, 50 population controls were selected for investigation.

With the permission and collaboration of the hospitals from which patients were identified, the medical records of each eligible patient were obtained and abstracted by 2 qualified physicians. These abstracts were reviewed by the field manager; the rate of agreement was 99%.

Of the 25 patients, all but 1 (96%) were successfully interviewed; 1 was psychotic. One of the 75 selected controls refused to cooperate; thus the participation rate for controls was 98.7%.

Thirty-nine subjects (nearly 40%) were reinterviewed by the field manager. The rate of agreement on all questions was 96%. The major discrepancies were found in the sections on diet and interval since last pregnancy. Twenty interviews, also tape-recorded and checked with completed forms, showed an agreement rate of over 99%.

Data from the abstracts and interviews were transmitted onto coding sheets and submitted to NCI for key punching. Frequency distributions were generated for all data items and reviewed during a meeting at NCI in November 1983 attended by staffs of the Capital Hospital, Cancer Institute, and NCI; the group decided on minor modifications of both forms in preparation for the full-scale study and on changes in methods for control selection. Although it was decided by this group that matching on interval since last pregnancy was necessary, results of the pilot study emphasized the difficulties of accumulating such a control series among hospitalized patients. Thus procedures were developed for incorporation of such a matching factor into the selection of population controls by visits to street offices supplemented with visits to neighborhood family planning clinics and work health units.

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A Pilot Vitamin Intervention Trial in Linxian, People's Republic of China [1, 2]

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ABSTRACT—A 24-week pilot study of daily or weekly multiple vitamin supplementation among 852 adults in Linxian, where the rate of esophageal cancer is exceptionally high, demonstrated the feasibility of an intervention trial in this population. Compliance, when judged by pill count, was high for both frequencies of pill use. Only 2% of the subjects refused to take any pills, and, among pill takers, over 95% were reported to be taking most of their pills at the end of the study. Biochemical confirmation of high compliance was demonstrated in urine and blood tests, which showed markedly improved vitamin levels after supplementation. Results of the pilot study indicated that a system in which barefoot doctors were used in pill distribution was effective and that established field operating procedures for a full-scale intervention trial in this area were acceptable.—Natl Cancer Inst Monogr 69: 19–22, 1985.

The world's highest incidence of esophageal cancer occurs in Linxian, a rural county in North Central China with a population of 800,000 (*1, 2*). Reasons for the high rates of this cancer are unknown, but the population may be prone to specific carcinogenic exposures because of deficiencies of multiple nutrients, especially vitamins and minerals (*1–5*). Epidemiologic studies in various parts of the world indicate that patients with esophageal cancer and high-risk populations have often had nutritionally poor diets (*6–9*). Experimental evidence also suggests that animals with certain nutrient deficiencies are more susceptible to the induction of cancer by chemicals and that supplementation with micronutrients can inhibit tumor formation (*10–13*). A nutrition intervention trial is planned for Linxian for further evaluation of the role of dietary nutrients. This paper gives the results of a pilot study with which we assessed the feasibility of such a trial in the Linxian general population. The pilot study, in which participants were enrolled for 6 months, provided us with an opportunity to establish and evaluate an organizational framework for the investigation, assess compliance of the subjects to one of several pill-taking regimens, and determine nutritional status before and after supplementation.

SELECTION OF PARTICIPANTS

The pilot study was conducted in 2 of Linxian's northern communes (Yaocun and Rencun). From these communes, 21 production teams[11] were randomly selected, and local health and government officials were contacted to enroll adults 40–69 years old in the study. Table 1 shows the populations in these teams. Among the total of 937 adults aged 40–69 listed in team rosters from the 1982 census, 852 were enrolled in the trial; reasons for nonparticipation are also given. Only 23 persons (2.5%) refused to participate. The others were judged ineligible because of existing illness, temporary relocation, or other reasons. We determined ineligibility by a screening interview during which the trial was explained, informed consent was sought, and a history of medical conditions (including prevalent cancer) was requested that would exclude persons from entry into the trial.

PILL DELIVERY SYSTEM

The 21 production teams were divided into groups I–III of 7 teams each. All persons in each group received a packet containing 28 pills (4 rows of 7 pills in a sealed punch-out pack) at the beginning of the study period. One-A-Day Vitamins (Miles Laboratories, Inc., Elkhart, Ind.) were used. Those in groups I and II were instructed to take 1 pill daily in the morning hours. Participants in each 4-week period were given a new pill pack and the old one was collected. Persons in group I were also visited by the distributor every week and asked about their pill-taking. Persons in group III were instructed to take a pill only once a week. The distributor visited these individuals every week to witness the pill-taking. The number of enrollees in the 3 groups were 319, 292, and 241, respectively.

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[11] Counties in rural China are hierarchically divided into communes, production brigades, and production teams. The total population of a typical team is about 200.

TABLE 1.—*Total populations, No. of participants, and reasons for nonenrollment in the pilot trial*

Population	No.	Percent
Aged 40–69 yr	937	100
Enrolled	852	90.9
Nonenrolled	85	9.1
Ineligible[a]	46	4.9
Not located[b]	16	1.7
Refused	23	2.5

[a] Subjects were ineligible because of prevalent illness, including cancer, or for other reasons.

[b] These people were working outside Linxian and had no fixed mailing address.

The distributors were health station members (barefoot doctors) employed by the local production brigades. The barefoot doctors were supervised during the study by a field officer from the Cancer Institute, Chinese Academy of Medical Sciences, who held monthly sessions to discuss procedures and problem areas.

FOLLOW-UP AND COMPLIANCE RATES

The percent of enrolled participants lost to follow-up for each month during the course of the 24-week trial among the 3 groups is given in table 2. By "lost to follow-up," we mean that individuals were not available to participate in the trial that month. Reasons for unavailability were death, the development of cancer or other debilitating diseases occurring among participants, or relocation from the study area (almost always for work-related purposes). The percentages are not monotonically increasing over time because some participants who moved away from Linxian later returned and were again available as subjects or participants. At the end of the nearly 6-month trial, losses were about 3%, with 97% of all subjects still eligible to participate.

Table 3 gives the percent of enrolled participants (after adjustment for loss to follow-up) who refused to take any pills and returned the packets unopened. At the end of the study period, these refusal rates were 2.5% for those scheduled to take pills daily, whereas all the 241 persons in the weekly group took their pills.

Among those taking at least some pills, over 95% were taking (as judged by counting unused pills) most of the distributed pills by the end of the trial (table 4). For daily users, the percentage of pills taken tended to increase slightly over time.

TABLE 2.—*Percent of participants lost to follow-up during the 6-mo trial*[a]

Study group	4-wk period					
	1	2	3	4	5	6
I Daily pill/monthly visit	1.6	1.3	2.5	4.1	4.1	3.5
II Daily pill/weekly visit	1.7	0.0	1.0	2.1	2.1	3.1
III Weekly pill						0.8

[a] *See* text for definition of "loss to follow-up." The percentages are cumulative but do not increase monotonically because some enrollees who left the study area later returned and were again eligible for participation.

TABLE 3.—*Percent of participants who refused to take any pills in monthly allotment during the 6-mo trial*

Study group	4-wk period					
	1	2	3	4	5	6
I Daily pill/monthly visit	0.0	1.6	1.6	2.0	2.6	2.6
II Daily pill/weekly visit	0.0	3.1	3.1	2.8	2.4	2.5
III Weekly pill						0.0

In addition to counting unused pills, we also assessed compliance by urinalysis. We administered loading-dose tests to randomly selected participants to measure urinary riboflavin before pills were taken and at either 3, 5, or 9 weeks after the start of supplementation. Analyses of the before and after supplement data for individual participants are ongoing. However, of the analyses completed, average group levels of riboflavin are markedly higher postsupplementation (table 5).

NUTRITION ASSESSMENT

Nutrition assessments were made by assays of blood and urine samples and dietary and anthropometric information collected in April just before the start of supplementation and in August (4 mo later). The assessments were made on 100 randomly selected individuals taking pills daily and, for comparison, on 51 individuals of similar ages from other teams in the communes. High-performance liquid chromatography analyses of serum for retinol, beta-carotene, and tocopherol are being conducted, and red blood cells are being assayed for glutathione reductase activity (a more sensitive measure of riboflavin status than provided by urinary tests) and for selenium levels. Other studies in

TABLE 4.—*Percent of pill takers taking at least 80% of the pills in the monthly pill packs during the 6-mo trial*

Study group	4-wk period					
	1	2	3	4	5	6
I Daily pill/monthly visit	89.5	82.8	92.1	96.7	96.6	95.0
II Daily pill/weekly visit	95.1	94.3	95.7	98.6	97.1	97.1
III Weekly pill						97.5

TABLE 5.—*Average riboflavin in 4-hr urine samples before and during the pilot trial*

Time of specimen collection	No. of specimens	Mean urinary riboflavin, μg[a]
Before	116	756
After 3 wk	40	1,362
" 5 wk	44	1,423
" 9 wk	32	1,368

[a] Four-hour excretion was measured after each individual took a 5-mg loading dose of riboflavin.

TABLE 6.—*Average fat-soluble vitamin levels (ng/100 μl) in plasma obtained before and during the pilot trial among daily pill takers and controls*[a]

Vitamin	Daily pill takers (group II)		Controls	
	April (100)	August (90)	April (51)	August (45)
Retinol	23.8± 9.5	44.6±11.4[b]	26.7±12.8	27.7± 8.1
Alpha-tocopherol	700±229	931±208[b]	737±219	793±159
Beta-carotene	10.7± 8.1	15.9±12.6[b]	11.8± 7.3	11.1± 5.6
Alpha-carotene	2.0± 2.2	3.8± 3.2[b]	1.5± 2.1	2.8± 1.8[b]

[a] Values are expressed in mean ± SD. *Numbers in parentheses* are No. of participants or controls.

[b] Level is significantly different from corresponding April level ($P < .01$).

progress include levels of ascorbic acid in plasma and urine, urinary niacin and thiamin, and serum zinc and copper.

Preliminary data from the high-performance liquid chromatography analyses show increased levels of retinol and vitamin E (both included in the One-A-Day pills) among daily pill takers but little change among the controls [table 6; *see* (*14*) for a detailed description of the methods used in these analyses]. Also, levels of beta- and alpha-carotene (not included in the pills) increased among the supplemented group, as did those of alpha-carotene among the controls, which is consistent with the higher dietary intake of vegetables in summer than in spring. Reasons for the lack of increase in beta-carotene levels among the controls are not clear.

DISCUSSION

From the results of the pilot study we determined that a vitamin intervention trial would be well accepted by the Linxian population. Compliance, as judged indirectly by pill count, was exceptionally high, with nearly all the participants taking almost all of their pills. Of course, the disappearance of a pill from the packet is no guarantee that the pill was actually taken. However, the barefoot doctors knew of no one who was disposing of the pills without taking them. Furthermore, our ongoing analyses provide biochemical confirmation from urine (reflecting recent pill-taking) and blood tests (reflecting longer term pill-taking) that compliance was high. The barefoot doctors also reported that the participants liked taking the vitamins, and the percentage of pills consumed showed a slight increase over the duration of the trial. The pilot study also indicated that compliance was highest for weekly pill-taking, but the differences between daily and weekly compliance rates were so small that daily ingestion, which is superior from a nutritional point of view, would be preferable in a larger study. Weekly rather than monthly visits by the barefoot doctor also seemed to improve compliance slightly among daily pill takers, but the gains do not seem large enough to warrant the extra time and cost of these more frequent visits over a long duration.

The pilot study provided us the opportunity to establish an organizational system which can be readily expanded to accommodate a larger trial. Local government officials actively supported the trial and provided liaison between scientific staff from Beijing and barefoot doctors from the production brigades. The participation of the barefoot doctors proved to be practical and efficient, and the high compliance appears to be attributable to the rapport between the barefoot doctors and the villagers. Also confirmed was the fact that available census records could be used for the identification of study populations and for sampling purposes. It was not known before the trial how receptive persons would be to donating blood for analyses, and there was concern that many villagers would refuse. However, they cooperated and nearly one-third of the population enrolled in group II donated and gave about 6–8 ml blood.

The results of this project indicated that China–U.S. collaboration was effective despite the distances separating the 2 countries and differences in language and culture. Periodic visits of the National Cancer Institute staff to Beijing and Linxian and of Chinese Academy of Medical Sciences staff to Bethesda and other centers in the U.S have helped ensure close communications among investigators. Although some problems arose, including delays in arrangements for laboratory analyses, the major concerns were resolved satisfactorily.

Further analyses of the collected data are under way so that we can characterize more fully the nutritional status of the study participants and examine the correlation among the several micronutrient measures. Nevertheless, the available results are sufficient to indicate to us that a large-scale vitamin intervention trial conducted with mechanisms similar to those developed in the pilot investigation is logistically feasible in the Linxian population.

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Nutritional Status of the High Esophageal Cancer Risk Population in Linxian, People's Republic of China: Effects of Vitamin Supplementation [1, 2]

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ABSTRACT—Plasma levels of nutrients in 196 individuals were assayed as part of a study of the feasibility of a nutrition intervention trial in Linxian, a county in North Central China with exceptionally high rates of esophageal cancer. High-performance liquid chromatography analyses of samples collected in April 1983 showed low (relative to United States standards) base-line levels for retinol, alpha-tocopherol, and beta- and alpha-carotene. Repeat sampling in August 1983 revealed significantly increased plasma levels of retinol and alpha-tocopherol among those who had in the interim received daily supplementation with multivitamin pills containing the Recommended Dietary Allowance levels of those nutrients but not among those without supplementation. Levels of carotenes, which were not included in the pills, tended to increase regardless of supplementation, consistent with seasonal variations in availability of carotenoid-containing foods. Atomic absorption spectrophotometry analyses showed essentially normal levels of copper and zinc in plasma. Neither was affected by vitamin supplementation (the pills did not contain minerals) nor seasonal variation. The data are generally consistent with prior biochemical surveys in indicating marginal or low status of several nutrients in Linxian and in showing that supplementation with vitamins can effectively raise blood nutrient levels.—Natl Cancer Inst Monogr 69: 23-27, 1985.

Linxian, a County in Henan Province in northern China, is a high EC risk area with an annual mortality rate of over 100/100,000. Epidemiologic and experimental research during the past 25 years has pointed to the importance of dietary factors in the etiology of this cancer. Extensive work has been performed by investigators in Linxian to detect suspected carcinogens and their precursors in food and drinking water (*1, 2*). In Linxian, as in many high EC risk areas (*3, 4*), nutritional deficiency is believed to be an important contributing factor to the development of this cancer. Vitamin deficiencies in particular have been suspected on the basis of dietary intake patterns and results of biochemical analyses (*2, 5*). A joint U.S.–China nutrition intervention study on EC in Linxian is being initiated so that the hypothesis that nutritional deficiencies are contributing factors to EC can be tested. This report deals with some of the results concerning vitamin and mineral nutrition obtained during a feasibility study in 1983.

MATERIALS AND METHODS

Collection and handling of blood samples.—The design and many results of this feasibility study are detailed elsewhere in this monograph (*6*). Villagers, who were 40–69 years old and placed in randomly selected production teams, were enrolled in a trial and given multivitamin pills daily (One-a-Day Brand, Miles Laboratories, Elkhart, Ind.) containing the Recommended Dietary Allowances for most vitamins. Blood samples were taken from 100 individuals in April (group I) before supplementation began. Repeat samples were taken from 90 of them the following August. In addition, blood samples were collected in April from 45 persons (group II) with esophageal dysplasia, a precursor lesion for EC. Repeat blood samples were obtained for 39 in August after approximately 4 months of supplementation as described for group I. For comparison, blood samples were also collected from 51 normal unsupplemented individuals (group III) in April; repeat samples were obtained from 45 of them in August.

The blood samples were collected in polyethylene tubes containing EDTA as an anticoagulant. We stored the samples on ice and within 2 hours centrifuged them at 2,000 revolutions/minute for 10 minutes to separate erythrocytes from plasma. The plasma samples were divided and stored in small vials at −30° C in a freezer. In November, some of the samples were packed in Dry Ice and delivered to the New Jersey Medical School where the samples were stored at −70° C before analysis.

Analyses.—The fat-soluble vitamins were analyzed by a newly developed HPLC procedure (*7*). After addition of an internal standard (alpha-tocopherol acetate), the 0.1-ml plasma sample was mixed with 0.1 ml ethanol and 0.23 ml hexane. The hexane phase was removed and dried under nitrogen, and the residue was dissolved in 50 μl ethanol. A 40-μl sample was injected onto a Radial-Pak C18 column and eluted with an isocratic solvent system of methanol–acetonitrile–chloroform (25:60:15) at a flow rate of 1.5 ml/minute. Quantitation was based on peak area ratios according to the method described in (*7*).

ABBREVIATIONS: EC=esophageal cancer; HPLC=high-performance liquid chromatography.

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[6] We thank the health organizations and their staffs in Linxian for their assistance.

The contents of zinc and copper in the plasma samples were analyzed by atomic absorption spectrophotometry (Dr. John Bogden, University of Medicine and Dentistry of New Jersey, Newark, N.J.) as described in (*8*).

RESULTS

The HPLC conditions used for the present study allowed the separation and simultaneous determination as shown in figure 1 of retinol (peak a), alpha-tocopherol (f), lycopene (h), alpha-carotene (i), and beta-carotene (j), in a single HPLC run. The results of the retinol analysis are illustrated in figure 2. Before supplementation in April, the plasma retinol levels (mean ± SD) of groups I, II, and III were 23.8 ± 9.5, 23.6 ± 10.5, and 26.7 ± 12.8 ng/100 μl, respectively. In these groups, 35–40% of the individuals had plasma retinol levels lower than 20 ng/100 μl, which, in nutritional surveys, are considered to be either low or deficient (*9*). After supplementation, the plasma retinol levels of groups I and II increased significantly ($P<.001$) to 44.6 ± 11.4 and 40.3 ± 11.4 ng/100 μl, respectively, in August. The individuals in group III did not receive the supplement and showed no significant change in plasma retinol levels in August (27.7 ± 8.1 ng/100 μl).

The plasma alpha-tocopherol levels were 700 ± 229, 723 ± 274, and 737 ± 219 ng/100 μl for groups I, II, and III, respectively, in April (fig. 3). About 55–64% of the individuals in these groups had values lower than 700 ng/100 μl, values considered to be either low or deficient in nutritional surveys conducted in Western countries (*9*). After supplementation, the values increased significantly to 931 ± 208 ($P<.001$) and 867 ± 224 ng/100 μl ($P<.01$) in groups I and II, respectively. Group III showed a mean value of 793 ± 159 ng/100 μl for the samples collected in August, which was not significantly different from that seen in April.

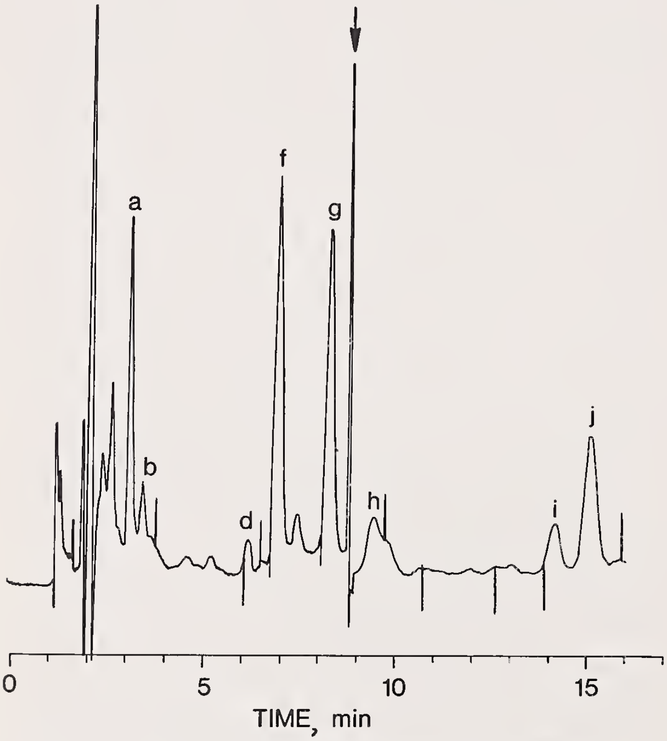

FIGURE 1.—HPLC separation of vitamins and carotenoids. Peak identifications: a) retinol; b) zeaxanthin (tentative); d) beta- and gamma-tocopherol (tentative); f) alpha-tocopherol; g) alpha-tocopherol acetate; h) lycopene; i) alpha-carotene; and j) beta-carotene.

The beta-carotene levels were 10.7 ± 8.1, 8.3 ± 6.0, and 11.8 ± 7.3 ng/100 μl for groups I, II, and III, respectively, in April (fig. 4). In August, the corresponding values changed to 15.9 ± 12.6, 13.1 ± 8.1, and 11.1 ± 5.6 ng/100 μl. The alpha-carotene levels for groups I, II, and III were 2.0 ± 2.2, 1.2 ± 1.4, and 1.5 ± 2.1 ng/100 μl in April and 3.8 ± 3.2, 4.0 ± 5.0, and 2.8 ± 1.8 ng/100 μl, respectively, in August (fig. 5). In comparing the carotenoid levels of the samples obtained in April and August from each group, we observed significant increases ($P<.01$) in all the August samples with the exception of the beta-carotene levels of group III. Lycopene, a carotenoid commonly present in human plasma samples in the U.S., was found in only 14% of the August and in none of the April samples. This probably reflected the pattern of seasonal consumption of lycopene-containing foods such as tomatoes. On the other hand, possibly due to the corn-based diet, the plasma samples contained high quantities of zeaxanthin, which was eluted slightly slower than retinol (data not shown).

Zinc is known to be involved in vitamin A metabolism and, therefore, plasma zinc and copper levels were analyzed. The plasma zinc concentrations were 84 ± 11 μg/dl ($n = 98$) and 83 ± 13 μg/dl ($n = 100$) in samples collected in April and August, respectively. Among the 198 samples analyzed, 22 had values less than 68 μg/dl, so that 11% would be considered marginally deficient by U.S. standards (*10*). That normal copper values were observed in the plasma samples having low zinc values suggested that the low zinc levels were not due to disease. The plasma copper levels were 100 ± 18 μg/dl ($n = 98$) and 113 ± 24 μg/dl ($n = 99$) in samples collected in April and August, respectively.

DISCUSSION

The present work demonstrated that after several months of supplementation with a daily intake of 5,000 IU of vitamin A and 15 IU of vitamin E (levels of Recommended Dietary Allowances), plasma levels of these vitamins were significantly elevated; thus these nutrients can be adequately absorbed if made available to the Linxian population. No change was observed for the group who did not receive the supplements. However, plasma alpha- and beta-carotene levels were higher in samples collected in August than those in April in most groups, even though the vitamin pills did not contain carotenes. It is likely that the differences in carotene levels between August and April reflect seasonal variation in the dietary intake of these nutrients. The lack of detectable seasonal changes in the retinol and alpha-tocopherol levels of group III suggests that: 1) The dietary intake of these vitamins was not significantly increased in August, and 2) the increased carotene levels had not saturated the body's store of

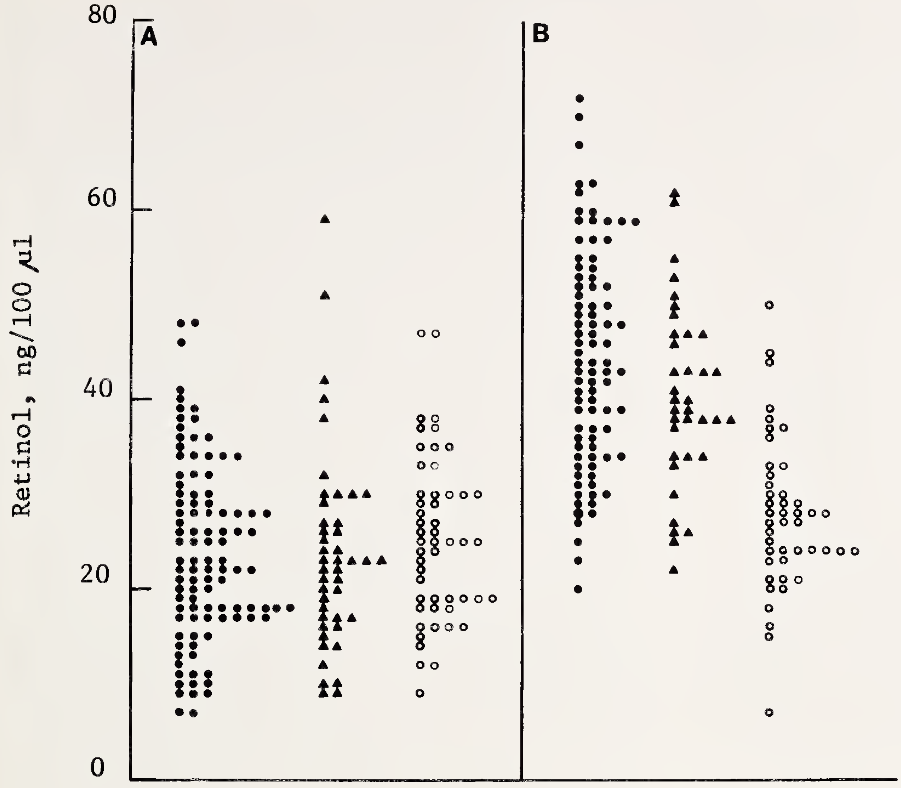

FIGURE 2.—Plasma retinol levels. Samples were collected in April (A) and August (B) of 1983 from individuals in group I (*closed circles*), II (*triangles*), and III (*open circles*).

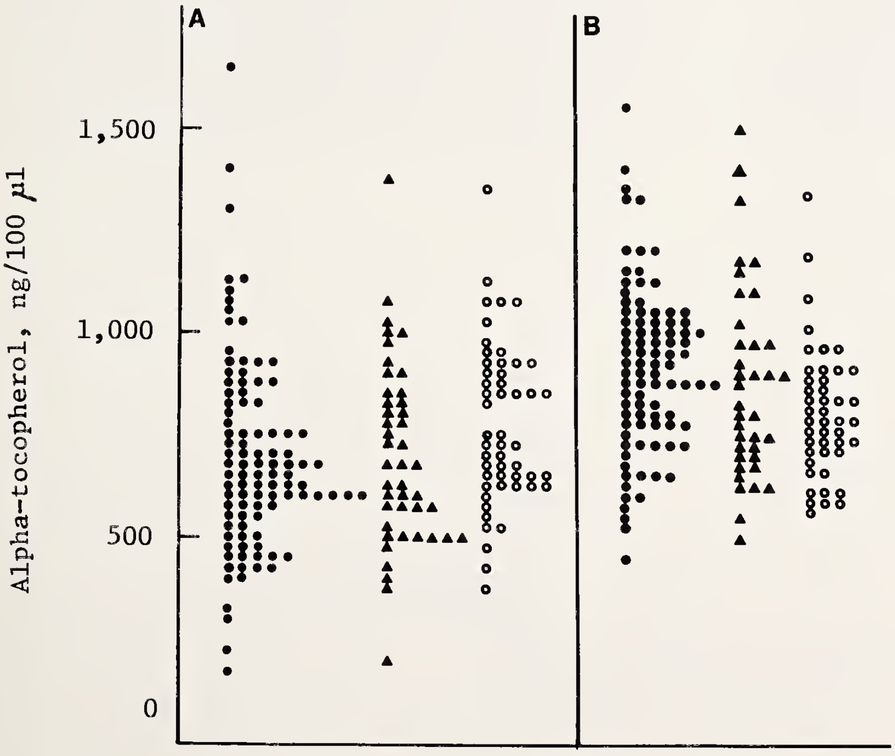

FIGURE 3.—Plasma alpha-tocopherol levels. Samples were the same as for figure 2.

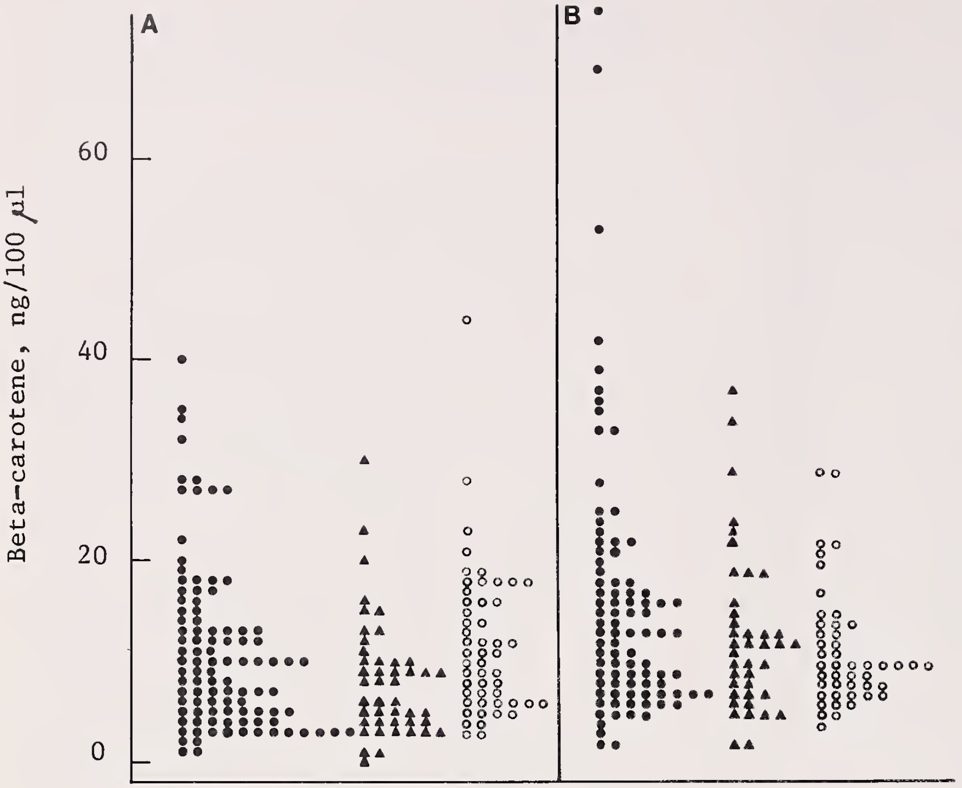

FIGURE 4.—Plasma beta-carotene levels. Samples were the same as for figure 2.

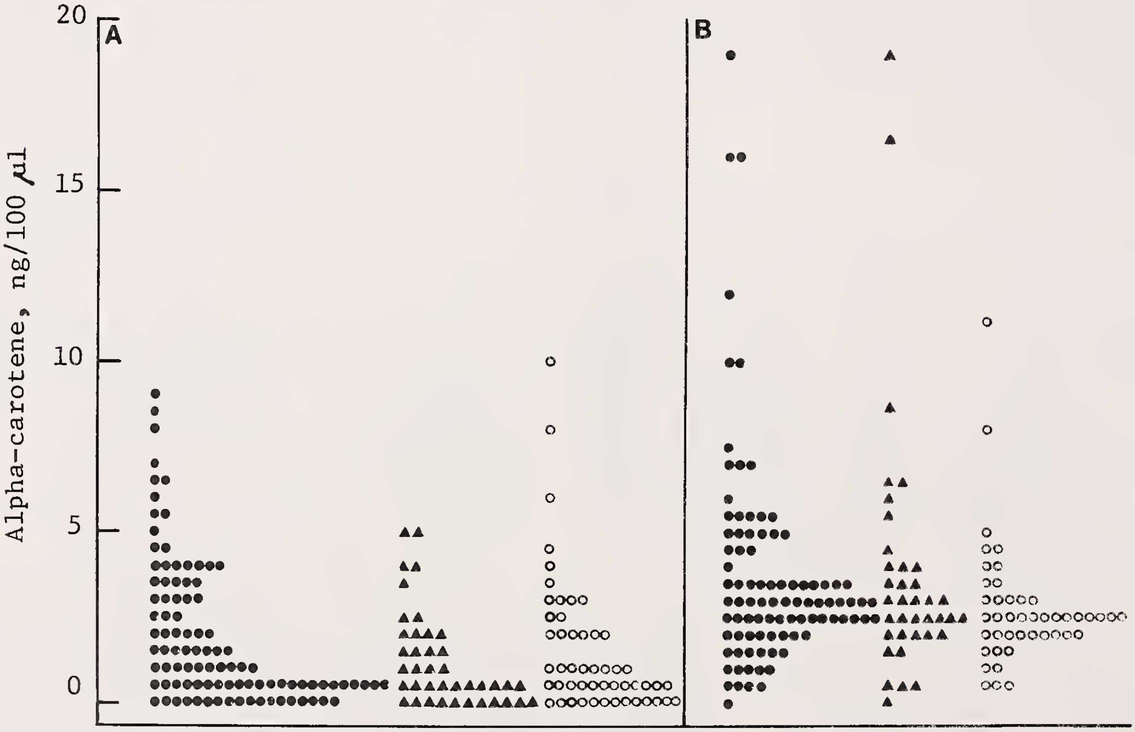

FIGURE 5.—Plasma alpha-carotene levels. Samples were the same as for figure 3.

vitamin A and thus were not reflected in the plasma retinol levels.

The plasma retinol levels we observed are comparable to and slightly lower than those obtained in a September 1980 survey in Linxian's Chengguan Commune. An average plasma level of 27 ng/100 μl was found then, with about 20% of the individuals having levels below 20 ng/100 μl (*5*). As the seat of the county government, Chengguan is generally considered to be a slightly more affluent area in comparison to the communes in northern Linxian, and this factor may contribute to the slight differences observed. However, the beta-carotene levels are much lower than those of total carotene determined by a spectrophotometric method (*5*). From our analysis, the total carotene level, which is dependent on diet, can easily be five to ten times higher than the beta-carotene level. This points to the importance of our measuring specific carotenes, particularly because they may differ in biologic effectiveness. The observed low plasma retinol, alpha-tocopherol, and beta-carotene levels are consistent with results from dietary surveys showing low dietary intake of animal products, oil, and vegetables (*5*). Deficiencies in riboflavin and ascorbate were also observed previously (*5*), but none for copper were indicated from the present or previous work (*11*). Previous reports indicated low zinc nutritional status (*12*), but we noted little indication of deficiency.

The base-line plasma retinol and alpha-tocopherol levels in the patients with esophageal dysplasia (group II) were not lower than corresponding values for normal individuals (groups I and III). This finding is surprising if the nutrients are in fact related to EC risk, inasmuch as dysplasia is a well-recognized precursor to EC (*1, 2, 12*). The gains in retinol and alpha-tocopherol blood levels following supplementation were less for those with than without dysplasia and raise the possibility that these patients may be less able to absorb the nutrients. Mean carotene levels, on the other hand, were significantly lower in group II (dysplasia) than group I individuals in April but not in August. Further study is needed for clarification of those characteristics, including dietary patterns of patients in group II, that lead to their high risk of EC.

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Some Considerations in the Design of a Nutrition Intervention Trial in Linxian, People's Republic of China [1, 2]

William J. Blot [3] *and* Jun-Yao Li [4]

ABSTRACT—Various issues pertaining to the design of a nutrition intervention trial in Linxian, a county in North Central China where esophageal cancer rates are extraordinarily high among a population with chronic deficiencies of multiple nutrients, are addressed. Two target populations are idenified: One is a group of patients diagnosed with severe esophageal dysplasia, the other is the general population of the high-risk area. Interventions involving the supplementation of each group with vitamins and minerals are described, and a rationale is provided for the selection of nutrients and choice of dose levels. Several potential statistical designs are evaluated, with particular emphasis on the balancing of gains in specificity afforded by full and fractional factorial designs against their potential loss in sensitivity compared with the simplest design involving a placebo versus a multiple vitamin and mineral supplement.—Natl Cancer Inst Monogr 69: 29–34, 1985.

The world's highest incidence of EC occurs in parts of North Central China, particularly in Linxian, where 1 in 4 persons in some communes dies of this neoplasm (*1, 2*). Reasons for the exceptional risk of EC are not yet known, but the clustering may be related to increased exposure to specific carcinogens among a population unusually susceptible because of chronic nutritional deficiencies. Consistent evidence is now emerging from a number of analytic epidemiologic investigations conducted outside China that patients with epithelial cancers, including those of the esophagus, often had diets characterized by reduced intakes of certain foods, especially fruits and vegetables (*3–5*). This is in line with correlational data, which show also that areas of the world with elevated EC rates have corn or wheat as the dietary staple, with low intakes of riboflavin, ascorbic acid, niacin, zinc, and other nutrients (*6*). The resultant characteristic is a generally poor diet with marginal (although not necessarily clinically deficient) status for several nutrients. Existing data indicate that Linxian conforms to this pattern (*1, 2, 7–9*).

Observations in the laboratory suggest that the low nutrient intakes are related to the high risk of cancer; for a number of nutrients, deficiencies can enhance and supplementation can inhibit tumor development following exposure to known carcinogens. Included in the list of nutrients for which protective effects are thought to exist are retinol (*10*), beta-carotene (*11*), riboflavin (*12*), ascorbic acid (*13*), vitamin E (*14*), magnesium (*15*), molybdenum (*16*), selenium (*17*), and zinc (*18*). Intakes of each of these nutrients are thought to be at least marginally low in Linxian. However, the combined epidemiologic and laboratory evidence does not seem specific enough to us to single out 1 or 2 nutrients as being solely responsible for the clustering of EC in Linxian. Instead, a broader hypothesis that 1) multiple vitamin and mineral deficiencies may contribute to high rates in Linxian and 2) supplementation may reduce the cancer risk is raised.

During the past year, we and our colleagues (*19*) conducted a pilot study in Linxian to test the feasibility of launching a nutrition intervention trial to test this hypothesis. The pilot trial, described elsewhere in this monograph (*19*), indicates that a large-scale trial in Linxian is logistically feasible. Options for the design of this full-scale nutrition intervention trial are described herein. Considered are the issues of the population to be enrolled in the trial, the vitamin and mineral combinations and dose levels to be used in the supplements, the statistical design of the trial, and the end points to be measured.

DESIGN ISSUES

Target Population

Table 1 shows EC rates for Linxian and its northern communes where the intervention study is to take place. Similarly, adjusted rates for China and the U.S. are also listed that clearly demonstrate the substantial excess of EC in this population. Although rates of EC are extremely high in the general population of Linxian, a subgroup of persons with severe dysplasia of the esophagus has extraordinarily high rates. A mass screening survey in 1974 identified by cytology over 2,000 persons with severe esophageal dysplasia. Preliminary data on follow-up through 1982 indicate that their subsequent risk of EC may be three to four times greater than those without severe dysplasia.

In designing the intervention trial, we considered the possibility of limiting the target population to those with severe dysplasia. This option is attractive because the study size could be much smaller, the logistics of pill delivery would be easier, and the trial would cost less. Furthermore,

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ABBREVIATIONS: EC = esophageal cancer; RDA = Recommended Dietary Allowances.

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[2] Supported in part by Public Health Service contract N01-CP21012 with the Division of Cancer Etiology, National Cancer Institute.

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TABLE 1.—*Esophageal cancer mortality rates in Linxian among adults 40–69 yr old*

Area and population	Annual age-adjusted rate/10^5[a]
Total Linxian County	470[b]
Linxian's northern communes	760[c]
With dysplasia	1,775[d]
Without dysplasia	510[d]
China	56[e]
U.S. whites	5[f]
U.S. blacks	19[f]

[a] Rates are adjusted to the northern Linxian standard population in 5-yr age groups 40–69 yr.

[b] Data are for 1959–81 (Esophageal Cancer Institute, Lin County: Unpublished results).

[c] Data are for 1970–81 (Chinese Academy of Medical Sciences: Unpublished results).

[d] Rate is estimated on the assumption that the EC rate is increased 3.5-fold in persons with dysplasia and that persons with dysplasia comprise 20% of the study population.

[e] Data are for 1973–75 (*20*).

[f] Data are for 1970–75 and were obtained from the National Cancer Institute.

such a trial would be most efficient in the following sense: If the progression to EC follows a sequence from normal to hyperplastic to dysplastic to cancerous cells in almost all affected individuals [as has been postulated (*8*)], and if vitamin and mineral supplements are effective in reversing the dysplasia or at least in inhibiting the transformation to cancer, then treatment of only persons with dysplasia is sufficient to reduce the cancer problem in Linxian.

However, it may be that dysplasia is too advanced in the carcinogenic process for vitamin and mineral supplementation to be protective. There is also a practical problem of identification; dysplasia is often symptomless. The diagnostic procedure used in Linxian involves the subject's swallowing a balloon that is covered by a fine mesh net and attached to a 3-foot cord through which a measured volume of air is passed (after swallowing). The inflated balloon is then withdrawn, and cells are scraped as it ascends the esophagus. The withdrawn mesh is swabbed against a glass plate which is read microscopically for the cytologic diagnosis. Because the procedure, which can induce discomfort and vomiting, is unpopular with the local population, investigators have found it impractical as an ongoing screening tool for identifying large numbers of persons with dysplasia, although they have encountered some success in recent campaigns.

The possibility of the intervention coming too late and the practical difficulty of assembling large numbers of dysplasia patients argue against our limiting the trial to this subgroup. Instead, the alternative of a trial involving a fixed sample of persons with recently diagnosed prevalent dysplasia *and* a trial involving persons selected from the remainder of the Linxian population can be advanced. The latter trial has the advantage of covering the entire high-risk population. The pilot study conducted in Linxian established that this approach is feasible.

Type of Intervention

Selecting the interventions involves the choice of vitamins and minerals that we would administer and the dose levels of each nutrient. Listed below are the vitamins and minerals for which there is some suspicion [usually based on biochemical evidence (*1, 2, 7–9*)] of deficiency among the Linxian population:

Vitamins	Minerals
Ascorbic acid	Magnesium
Beta-carotene	Molybdenum
Niacin	Selenium
Retinol	Zinc
Riboflavin	
Vitamin E	

Laboratory evidence indicates that each[5] of these elements may lower the risk of chemically induced cancer in experimental animals (*10–18*). Although the nutrient in which the Linxian diet appears to be most deficient is riboflavin, the general pattern is one of overall poor nutrition with low intake of multiple micronutrients. A primary option for the interventions is thus multiple vitamin and mineral supplementation, which would permit a direct test of the hypothesis that correction of these multiple and possibly interrelated deficiencies may reduce cancer risk. All the nutrients listed above would be included in the trials. Several different design options have been considered to enable us to separate the effects among these individual nutrients or groups of nutrients.

The selection of an appropriate dose for each nutrient depends partly on the perspective from which the trials are viewed. If seen as tests of the hypothesis that the nutritional deficiencies in Linxian have contributed to its high rates, then the doses need only be large enough to remedy the deficiencies. Thus doses close to the U.S. RDA should be sufficient. If, however, one also views the trials in the more general context as chemopreventive tests of the inhibitory effects of vitamins and minerals, and if there is an approximately linear dose–response relationship, with higher doses affording greater cancer reduction, then the doses should be set as high as possible without resulting in toxicity, other adverse side effects, or antagonistic competition between multiple nutrients. Thus for several nutrients, doses many times higher than the RDA would be considered.

The identification of an appropriate high dose level for each nutrient is difficult, however, because of lack of information on how the metabolism of nutrients is interrelated and on the shape of the dose–response curve in human populations. Epidemiologic investigations of several epithelial cancers do suggest that there is an inverse

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[5] The evidence for niacin appears most limited, but a promoting action of niacin deficiency has been reported in 1 carcinogenesis experiment in South Africa (*21*), and diets marginally deficient in lipotropes, niacin, and amino acids have been implicated in promoting hepatocarcinoma in another (*22*).

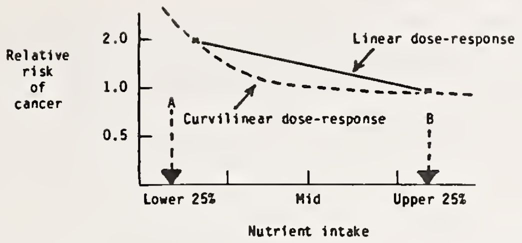

FIGURE 1.—Schematic representation of the possible relationship between nutrient intake and EC risk.

association with consumption of certain foods, particularly fruits and vegetables. For EC, 1 case–control study among black males in Washington D.C. showed approximately a twofold difference in risk between those in the upper versus lower third of fruit and vegetable consumption (*3*). In New York State, others (*4*) found roughly a twofold difference between the upper and lower quantiles of an index of vitamin A consumption. These findings, typical of those for other cancers, suggest that the nutrient–cancer relationship may be similar to the ones shown schematically in figure 1. However, whether the relationship is linear (the solid line) or follows some other form (such as the curvilinear dotted line) is unknown. Typically, the animal experiments have used high doses and thus provide some support that these doses may be protective,[6] but such experiments have not been large enough for us to distinguish between different functional forms of dose–response models.

An option investigators have actively considered for the Linxian trials is to provide dose levels high enough to move the nutrient status of the Linxian population from point A to point B on the diagram in figure 1. Thus the current deficiencies would be corrected and average nutrient status would be shifted to approximately that of the upper 10 or 20% of the U.S. population. The doses of most nutrients needed to effect this change are estimated to be about 1.5 to 3 times the U.S. RDA. This option represents a compromise between the two views expressed earlier: The doses exceed the RDA and place the study subjects in the upper portion of the expected dose–response curve but are low enough to avoid problems of toxicity, nutrient interactions, or other unknown responses from exceptionally high levels.

Statistical Design

Several forms of the intervention trials have been assessed. Consideration has been given mostly to a design involving 2 groups (a multiple vitamin–mineral supplement vs. a placebo) and to several types of factorial designs involving 4 or more treatment groups.

We believe a 2-group trial (being the simplest) is the easiest to conduct, is likely to be the least expensive, and is the most powerful under a number of alternative outcomes. Such a trial is completely noninformative regarding the effects of the individual nutrients. From a public health point of view, however, knowledge that a readily available, safe, multiple vitamin–mineral supplement could reduce cancer risk would be an enormous advance even if it were not known which ingredients were most effective.

Although a factorial design yields a gain in specificity, permitting the separation of effects associated with individual factors and thus providing more useful etiologic information, it tends to be more expensive because several types of pills need to be formulated, and, more significantly, it can be less powerful.

Examples of how a factorial design can be less powerful than a 2-group design are shown in tables 2 and 3. The comparison in both tables is between the simplest factorial design, a 2×2 design evaluating factors A and B in a 4-group layout (placebo, A, B, AB), and a 2-group design (placebo, AB), with the total sample size the same for each design. In table 2, the total sample size is set at 2,000 and the base-line 5-year EC mortality rate at .089. In table 3, a sample size of 25,000 is used with a base-line rate of .025. These sample sizes are near the maximum available for the dysplasia and general population trials; the 5-year probabilities are approximately those currently experienced by persons with and without severe dysplasia in Linxian (*see* table 1).

The situations presented in tables 2 and 3 represent several possible outcomes. The first situation in table 2 assumes that there are separate protective effects (15, 20, or 25% reductions) associated with each of factors A and B and that together they are additive. For this situation, the factorial trial is clearly less powerful. In effect, the 2-group trial must detect differences of 30, 40, or 50%, whereas for either factor A or B, the factorial design has the harder task

TABLE 2.—*Statistical power calculations for a 4-group (placebo, A, B, AB) factorial vs. a 2-group (placebo, AB) design under several alternative outcomes: Dysplasia trial*[a]

Possible situation	Outcome: Percent decrease due to:				Power of:[b] Two-group trial	Power of:[b] Four-group trial to detect effect of:	
	Placebo	A	B	AB		A	B
I	0	15	15	30	.73	.30	.30
	0	20	20	40	.93	.46	.46
	0	25	25	50	.99	.64	.64
II	0	30	0	30	.73	.73	.05
	0	40	0	40	.93	.93	.05
	0	50	0	50	.99	.99	.05
III	0	30	30	30	.73	.32	.32
	0	40	40	40	.93	.50	.50
	0	50	50	50	.99	.71	.71
IV	0	30	30	0	.05	.05	.05
	0	40	40	0	.05	.05	.05
	0	50	50	0	.05	.05	.05

[a] Assumptions are: Type I error alpha = .05 (one-sided); base-line 5-year cancer rate = .089; total sample size = 2,000.

[b] We used the procedure described in (*27*) for the power calculation.

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[6] This is not always true. High doses of synthetic retinoids have promoted rather than inhibited carcinogenesis in several experiments (*23–25*). In another study, a high level of ascorbic acid promoted tumor development, whereas no effect was seen at a moderately high level (*26*).

TABLE 3.—*Statistical power calculations for a 4-group (placebo, A, B, AB) factorial vs. a 2-group (placebo, AB) design under several alternative outcomes: General population trial*[a]

Possible situation	Outcome				Power of:[b]		
	Percent decrease due to:				Two-group trial	Four-group trial to detect effect of:	
	Placebo	A	B	AB		A	B
I	0	10	10	20	.85	.38	.38
	0	15	15	30	.99	.66	.66
	0	20	20	40	.99	.88	.88
II	0	20	0	20	.85	.85	.05
	0	30	0	30	.99	.99	.05
	0	40	0	40	.99	.99	.05
III	0	20	20	20	.85	.39	.39
	0	30	30	30	.99	.69	.69
	0	40	40	40	.99	.92	.92

[a] Assumptions are: Type I error alpha = .05 (one-sided); base line 5-yr cancer rate = .025; total sample size = 25,000.

[b] See footnote *b*, table 2.

of detecting average differences of 15, 20, or 25%. In the second situation, only 1 of the 2 factors (factor A) is effective. In this instance, the factorial trial is as powerful as the 2-group trial because both trials need to detect the same average effect. Of course, the factorial design provides the considerable advantage of telling us that the effect is limited to A. In situation III, in which A and B protect, but no extra reduction results from their combination, the factorial design is again less powerful because the average effect it must detect is only about one-half as large as in the 2-group trial [for factor A, e.g., the average effect in the middle row is 1/2 × (40% + 0%) obtained from a comparison of A vs. placebo and AB vs. B]. In situation IV, the protective effects of A and B cancel each other in combination, and the factorial design is equally powerful but more advantageous because it can detect the negative interaction. Table 3 shows similar results for the general population trial.

The patterns in table 2 and 3 indicate that, for equal-sized trials, the factorial experiment can be less powerful, with the loss substantial when independent or even subadditive effects of the 2 factors are present. Such losses become even more pronounced for 2^3, 2^4, or higher order factorial designs because then the effect of the combined factor group is partitioned over an even larger number of factors. A further complication, more serious with the larger factorial designs, involves multiple comparisons. The 2-group trial always uses just 1 hypothesis test. On the other hand, a 4-factor factorial trial involves at least 4 tests, even when tests for interaction are ignored. Thus the interpretation of the trial is less clear if only one of the 4 tests is significant. Adjusting the type I alpha error levels will partly account for multiple comparisons, but such adjustments will result in further reduction in the power of the factorial compared with the 2-group trial.

One can raise the power of a statistical test by increasing its sample size. Thus the gains in specificity of a factorial trial can be obtained and the potential lack of sensitivity guarded against if a larger study can be conducted. In Linxian, the restrictions are fairly strong on the number of individuals with severe esophageal dysplasia available for enrollment. It appears that 2,000 may be the upper limit. Inasmuch as a 2-group trial of this size could identify only about a 40% or greater reduction in the 5-year EC rate with high probability (table 2), we propose the use of a 2-group (multiple vitamin–mineral supplement vs. placebo) design for the dysplasia trial. However, the number of persons available for participation in the general population trial is less restricted, and for this trial a factorial design seems preferable.

Several options for such a factorial design have been considered. It was readily apparent that a factorial design evaluating the 10 nutrients listed above (a 2^{10} design) was impractical. Alternative designs would combine or delete some nutrients, perhaps in the context of a fractional factorial design (*28*). A fractional design uses only a portion (usually one-half or one-fourth but possibly less) of all the possible treatment combinations of a full factorial design. The economy afforded by the fractional factorial design is at the expense of the lost ability for evaluation of certain interactions. In addition, there is some confounding of effects, but for one-half or one-fourth fractions of 2^4 or 2^5 or higher designs, all the main effects can still be adequately estimated.

Regardless of whether a full or fractional factorial design is used, some combination of nutrients must be made, i.e., a smaller number (preferably 3 or 4 or at most 5) of factors is necessary. The possibility of our eliminating some of the nutrients was considered, but this "cleaning" might be at the expense of a missed opportunity to identify a critically important contribution to high rates in Linxian. Furthermore, because one could argue in favor of maintaining each of the 10 nutrients to be studied, it is not easy to select the ones to be eliminated.[7] Thus combinations were considered.

TABLE 4.—*Possible combinations of nutrients for a full or fractional factorial design*[a]

Factor	Nutrients
A	Retinol Beta-carotene Zinc
B	Riboflavin Niacin
C	Ascorbic acid Molybdenum
D	Vitamin E Selenium

[a] A one-half replicate of a 2^4 factorial design with these factors would include the following 8 treatment groups: placebo, AB, AC, AD, BC, BD, CD, and ABCD.

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[7] Practical difficulties in formulating pills dictate that magnesium be eliminated because it requires the most bulk (400 mg) to achieve its RDA level.

Table 4 lists 4 such combinations of 9 nutrients (excluding magnesium). Factor A combines beta-carotene and retinol with zinc, a trace mineral which aids in the transport of vitamin A from liver stores (*29*). Factor B includes the B-vitamins deficient in Linxian (riboflavin and niacin). Factor C combines ascorbic acid and molybdenum, elements consistently found in low levels in Linxian. Both are thought to block the formation of nitrosamines (*16, 30*), compounds possibly involved in the initiation and promotion of EC in this area (*1, 2, 31*). Factor D consists of vitamin E and selenium. A recent evaluation of micronutrient levels in stored sera from individuals participating in a hypertension follow-up project suggests that low levels of selenium may be more important than are low levels of fat-soluble vitamins in cancer induction (*32*). A combination of selenium and vitamin E is advantageous because these strong inhibitors in carcinogenesis experiments have been reported to act synergistically (*33*).

With these factors, a full factorial design would involve the assignment of each participant in the trial to 1 of 16 groups. A more economical design seems preferable in rural Linxian, however. One option is use of a one-half replication of the 2^4 factorial. Such a design (an 8-group layout is shown in table 4) would permit testing of the main effects of all 4 factors, although two-way interactions between factors would be confounded with each other. Power would be lost under certain possible conditions (e.g., if the effects of each factor were additive) for this design compared with the simplest 2-group trial, but a trial with 25,000 participants could detect with fairly high power reductions of 20% from each nutrient (table 3). Another option involving a simpler design is a 2^3 factorial, in which factors C and D are combined. This design would allow the separation of effects of vitamin A–zinc and riboflavin–niacin from the remainder of the nutrients and could also assess interactions among vitamin A–zinc, riboflavin–niacin, and the remaining factor of several nutrients. Stated another way, it can examine consistency of the effects of 1 factor across all levels of the other 2, a feature not available with the fractional design. A final option is the use of a 2^2 design, e.g., combining factors B, C, and D. Such a design is more specific than the 2-group (multiple vitamin–mineral vs. placebo) trial in that it separates the influences of the vitamin A–zinc component, but it cannot distinguish differences among the nutrients within the second factor.

Choosing the optimal design for the population intervention trial among the several options is not an easy task because no design appears to be uniformly better than the others on all grounds. By balancing the competing statistieal concerns of sensitivity and specificity, given the limited sample size, and taking into account the logistical difficulties in formulating pills and delivering them in a rural setting like Linxian, we tended to favor the 8-group fractional factorial design described in table 4.

End Points

The primary end points in the dysplasia and general population trials are EC mortality and incidence. Although intermediate end points can be considered for full evaluation of the role of vitamins and minerals on cancer risk, the actual occurrence of cancer must be monitored. In addition to EC, total cancer mortality and incidence and total mortality will be ascertained. The period of ascertainment will be 5 years, the longest initial period currently available for collaborative National Cancer Institute contracts. If nutritional supplementation truly affects the late stages of the carcinogenesis process, a downward trend in incidence might be detectable within the 5-year period.

An intermediate end point will be assessed for those enrolled in the dysplasia trial. Repeat cytologic examinations will be made at periodic intervals (after 18, 36, and 60 mo of supplementation) so investigators can assess whether the vitamins and minerals have affected the prevalence of this precursor lesion, and, if so, whether the regression of the dysplasia is associated with reduced cancer incidence.

SUMMARY

The designing of a nutrition intervention trial in Linxian is a complex process; judgments must often be made in the absence of complete information. Nevertheless, it does appear possible for investigators to conduct trials that will advance knowledge of the etiologic role of vitamins and minerals, knowledge that may be of considerable importance in reducing the toll of cancer in this high-risk area of the world.

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T-Cell Lymphoma [1, 2]

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ABSTRACT—Of a total of 3,366 cases of malignant lymphoma in China reviewed histopathologically, T-cell lymphomas accounted for an average of 26.1% among all non-Hodgkin's lymphomas. However, the proportion of lymphomas of T-cell lineage varied in different parts of China, with the highest proportion (30–40%) along the east coast. Immunologic typing of 41 non-Hodgkin's lymphomas by the avidin-biotin-peroxidase complex technique revealed similar patterns. When serum antibodies to human T-cell leukemia virus were assayed in 462 normal men and 103 monkeys, 2–5% of the men and 8.4–15% of the monkeys were positive for antibodies to this virus. — Natl Cancer Inst Monogr 69: 35–37, 1985.

Retroviruses have been shown to be the causative agents of many animal leukemias. For a long time, however, investigators tried unsuccessfully to isolate a retrovirus from human leukemia. In 1980, Gallo and his associates (*1*) successfully isolated a retrovirus from an in vitro cultured T-lymphoma cell line, HUT-102, that was designated as HTLV. Two years later, Yoshida in Japan also isolated from a patient with adult T-cell lymphoma a retrovirus called ATLV (*2*). These retroviruses have been shown to be highly related antigenically.

We know that HTLV (or ATLV) is a type C, T-cell tropic RNA virus with reverse transcriptase. Its provirus DNA or the viral antigens, or both, can be detected in leukemia cells from patients with ATL and T-lymphosarcoma-cell leukemia. The HTLV-associated antibodies were present in most ATL patients in Japan and the Caribbean countries (*3, 4*). Thus HTLV (ATLV) has become a promising candidate in the viral etiology of human cancer.

In Japan, ATL is clustered in the southwestern part that has the climatic condition of high humidity, primarily in the islands of Kyushu and Shikoku (*5*). In China, the result of a nationwide survey of cancer mortality indicated that lymphoma occurs mainly along the Yangtze River (*6*), a region with the same latitude as the area in Japan where ATL is common.

In early 1982, our colleagues, who were then in the United States, were invited to visit NCI to discuss the possibility of conducting a collaborative epidemiologic study on T-cell lymphoma/leukemia. The ultimate goal was determination of whether HTLV is indeed responsible for the causation of certain types of human T-cell cancers.

The following is a brief summary of our preliminary studies of the composition of malignant lymphomas and HTLV-associated antibodies in the general population in China.

HISTOPATHOLOGIC STUDY OF MALIGNANT LYMPHOMAS

In December 1982, a slide review workshop was organized in Beijing under the auspices of the National Cancer Control Office. Pathologists from different parts of China were invited. Slides of pathologic specimens from all patients diagnosed as having malignant lymphoma from January 1978 through December 1982 in Shengyang, Nanjing, Beijing, Quigdao, Chengdu, Lanzhou, Kunming, and Nanning were pooled. A working standard for histopathologic diagnosis agreeable to participants was adopted. After the workshop, in the Spring of 1983, a small group of experienced pathologists went to Changsha, Wuhan, Fuzhou, and Haikou (Hainan Island) to review the relevant slides according to the same working standard. Slides of specimens of tissues from 3,366 patients with malignant lymphoma were reviewed. The results are shown in tables 1–3 and figure 1.

Table 1 shows that in China, among the patients with lymphomas, those with NHL are the most numerous. Unlike Western countries, Hodgkin's disease is relatively uncommon. Among persons with NHL, the ratio of T- to B-cell lymphomas is 0.38 to 1. On average, T-cell lymphomas account for 26.1% of all NHL; nonetheless, this type varies in its frequency from one place to another. A high frequency of T-cell lymphoma occurs in Shengyang, Nanjing, Beijing, and Qingdao (table 2). It is clear from

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Abbreviations: HTLV=human T-cell lymphoma/leukemia virus; ATLV=adult T-cell lymphoma virus; NHL=non-Hodgkin's lymphoma.

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[2] Supported in part by Public Health Service contract N01-CP21012 with the National Cancer Institute.

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TABLE 1.—*Percentages of Hodgkin's disease vs. NHL among lymphoma patients in selected areas in China, 1978–82*

Area	Total No. of cases	Hodgkin's disease		NHL	
		No.	Percent	No.	Percent
Shengyang	47	5	10.6	42	89.4
Nanjing	735	51	6.9	684	93.1
Beijing	118	7	5.9	111	94.1
Qingdao	289	24	8.3	265	91.7
Changsha	277	51	18.4	226	81.6
Chengdu	537	98	18.2	439	81.8
Lanzhou	103	7	6.8	96	93.2
Fuzhou	229	24	10.0	205	90.0
Kunming	98	11	11.2	87	88.8
Wuhan	264	44	16.7	220	83.3
Haikou	163	11	13.5	152	86.5
Nanning	506	34	6.7	472	93.3
Total	3,366	367	10.9	2,999	89.1

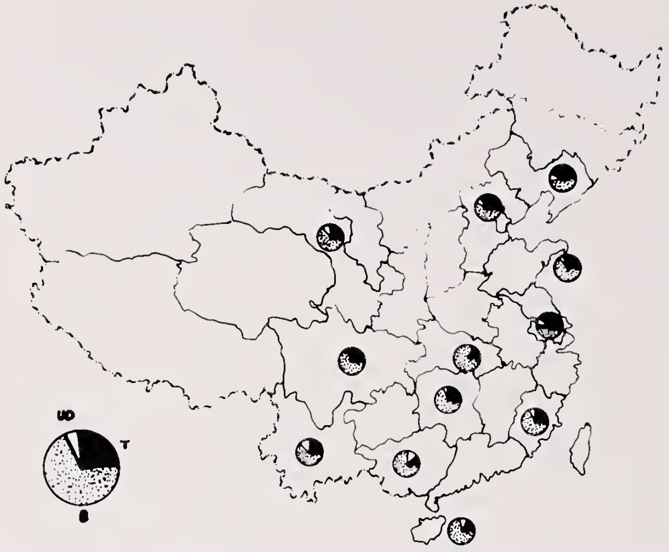

FIGURE 1.—Composition of non-Hodgkin's lymphoma in selected areas in China. T=T-cell, B=B-cell, UD=undetermined.

figure 1 that lymphomas of the T-cell type are more commonly seen along the east coast of China. According to the histopathology observed, 34% of these lymphomas are of the lymphoblastic type. Polymorphic lymphoma ranks next (table 3).

IMMUNOPATHOLOGIC STUDY WITH MONOCLONAL ANTIBODIES

A battery of monoclonal antibodies directed to the differentiation antigens of T- and B-lymphocytes were used in the immunologic typing of frozen sections following the avidin–biotin–peroxidase complex technique (*7*). So far, 41 cases have been examined. Again, B-cell lymphomas are most frequently encountered. Eleven of the 41 (26.8%) are lymphomas of the T-cell type. Histopathologically, 6 of the 11 T-cell lymphoma cases are of the lymphoblastic type, 4 are T immunoblastic sarcoma, and 1 is immunoblastic lymphadenopathy-like T-cell lymphoma. The lymphoblastic lymphoma is mainly of helper T-cell type (5 of 6), whereas the T immunoblastic sarcoma is mainly of the suppressor T-cell type (3 of 4). Of the balance, 21 (51.3%) were of the B-cell type, 1 (2.4%) was histiocytic, and 8 (19.5%) were undefined.

TABLE 2.—*T- and B-cell composition of NHL in selected areas in China, 1978–82*

Area	Total No. of cases	T-cell		B-cell		Undetermined	
		No.	Percent	No.	Percent	No.	Percent
Shengyang	42	20	47.6	19	45.2	3	7.2
Nanjing	684	275	40.2	390	57.0	19	2.8
Beijing	111	39	35.1	64	57.7	8	7.2
Quigdao	265	79	29.8	174	65.7	12	4.5
Changsha	226	61	27.0	157	69.5	8	3.5
Chengdu	439	118	26.9	316	72.0	5	1.1
Lanzhou	96	23	24.0	64	66.7	9	9.3
Fuzhou	205	46	22.4	138	67.3	21	10.3
Kunming	87	19	21.8	55	63.2	13	15.0
Wuhan	220	33	15.0	182	82.7	5	2.3
Hainan	152	22	14.5	112	73.7	18	11.8
Nanning	472	48	10.2	364	77.1	60	12.7
Total	2,999	783	26.1	2,035	67.9	181	6.0

HUMAN T-CELL LYMPHOMA/LEUKEMIA VIRUS-ASSOCIATED ANTIBODY ASSAY

Serum antibodies to HTLV were determined by enzyme-linked immunosorbent assay according to the method of Saxinger (*8*). A total of 462 serum samples from healthy blood donors were collected from 4 cities. Of the normal populations studied, 2–5% are positive for HTLV-associated antibody, as shown below:

Blood donors from	No. of positive samples/No. of samples examined	Positive rate, %
Beijing	6/198	3.0
Tianjin	3/85	3.5
Kunming	2/84	2.3
Shengyang	5/95	5.2

TABLE 3.—*Histologic types of T-cell lymphoma, all areas combined*

Histologic type	No.	Percent
Lymphoblastic lymphoma	266	34.0
Polymorphic lymphoma	172	22.0
Monomorphic lymphoma	133	17.0
Lymphoma with immunoblastic features	66	8.4
T-immunoblastic sarcoma	57	7.3
Clear cell type	46	5.9
Lennert	9	1.1
Skin T-lymphoma	14	1.8
T-small lymphocyte	8	1.0
Unclassifiable	12	1.5

Serum samples were also collected from rhesus monkeys (*Macaca mulatta*) for HTLV-associated antibody assay. One hundred three monkeys kept in the Institute of Medical Biology, Kunming, were examined. Twenty were normal untreated animals, and 83 had been given polio vaccine (for quality control of vaccine). The results indicated that 8.4% (7, vaccine treated) to 15% (3, untreated) of the monkeys are positive for HTLV-associated antibodies. The antibody titer is much higher than that in man, i.e., 1:1, 635 for the normal animals and 1:700 for the treated.

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Risk Factors for Breast Cancer in Tianjin, People's Republic of China [1, 2]

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ABSTRACT—Four hundred fifteen patients with breast cancer who were between 25 and 59 years old were interviewed. They were identified through a breast cancer screening program conducted by the Tianjin Cancer Institute during 1977–80. Controls were women who participated in the screening program but were free of breast cancer. The study confirmed early menarche, late age at first birth, and late menopause as major risk factors for breast cancer. Total duration of lactation was significantly associated with a reduction in its risk among parous women, but this was explained by higher parity among controls. No significant differences were observed between patients and controls in the amount of exposure to chest radiographs or use of hormones. — Natl Cancer Inst Monogr 69: 39–42, 1985.

Breast cancer rates vary widely among countries (*1*). The incidence of this disease is high in industrialized countries such as the United States, Canada, those in Western Europe, and Australia. Low rates are observed in Asia and tropical Africa, whereas intermediate rates are seen in Eastern and Southern Europe and South America. In Shanghai, the age-standardized incidence rate for breast cancer in females is 19/100,000, which is one-fifth the rate observed in white females in Los Angeles (*1*).

The epidemiology of breast cancer has been studied extensively in many populations, especially among high-risk Caucasians. Results from these studies consistently show early menarche, late AFB, and late menopause as the 3 major risk factors for breast cancer (*2–13*). Until recently, no data were available from the People's Republic of China for the evaluation of these risk factors in its female population. In this paper, we describe a case–control study of breast cancer in China in which these major risk factors were investigated. The study was conducted in Tianjin, an industrial city with breast cancer rates comparable to those in Shanghai (*14*).

MATERIALS AND METHODS

Incident cases of breast cancer were identified through a breast cancer screening program conducted by the Tianjin Cancer Institute during 1977–80. Approximately one-half of Tianjin's female residents between the ages of 25 and 59 years were examined for breast cancer during each of those years. Immediately following the termination of the screening program, all women first diagnosed by the screening program were contacted for participation in the study; a total of 415 were interviewed.

Controls were women who participated in the screening program and were free of breast cancer. For each patient interviewed, a control matched on nationality (Han, Muslim, or other), age (within 5 yr), and district of residence (Tianjin is administratively divided into 6 districts) was selected randomly from all those eligible.

Six trained interviewers questioned the women about their menstrual and reproductive histories, exposure to chest x rays, and use of hormones. The questionnaire data were analyzed by matched-pair methods (*15*). Pairs in which either the patient or the control failed to answer the relevant question were eliminated from the analysis. All statistical significance levels quoted (*P*-values) are one-sided.

RESULTS

Table 1, which presents the distribution of age at menarche, illustrates that early age at menarche was significantly associated with an increased risk of breast cancer. Women with menarches at 13 or younger had 2.2 times the risk of breast cancer compared with those whose menarche was delayed until they were 17 or older. Women whose menarche began when they were between 14 and 16 years old had an intermediate risk (1.6).

Delayed AFB and nulliparity were associated with a significantly elevated risk of breast cancer. The risk in nulliparous women was lower than that in women whose first children were born when they were over 35 but higher than those who gave birth when younger than that. The RR for breast cancer among nulliparous women compared with parous women with an AFB under 20 was 2.9 (95% confidence limits = 1.5, 5.8). Parous women with an AFB over 35 had an RR of 3.5 (95% confidence limits = 1.3, 9.2) compared with those with an AFB less than 20.

The RR of breast cancer by levels of AFB and age at menarche simultaneously are shown in table 2. In all 3 categories of menarcheal age, parous women whose AFB was more than 25 years had about twice the risk of breast cancer compared with those whose AFB was under 25.

ABBREVIATIONS: AFB = age at first birth; RR = relative risk(s).

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[5] We thank Dr. Malcolm C. Pike, Epidemiology and Clinical Trials Unit, Imperial Cancer Research Fund, Oxford, England, for his advice.

TABLE 1.—*Distribution of age at menarche, AFB, and age at menopause in patients and controls*

Factor	No. of patients	No. of controls	RR	95% Confidence interval
Age at menarche, yr				
≥17	86	130	1.0	
14–16	258	236	1.6	1.2, 2.3
≤13	71	49	2.2	1.4, 3.4
AFB, yr				
≤19	29	53	1.0	
20–24	135	185	1.3	0.8, 2.3
25–29	147	112	2.4	1.4, 4.2
30–34	45	30	2.7	1.4, 5.4
≥35	17	8	3.5	1.3, 9.2
Nulliparous	42	27	2.9	1.5, 5.8
Age at menopause, yr[a]				
≤44	11	18	1.0	
45–49	44	47	1.5	0.6, 3.7
≥50	85	70	2.0	0.9, 4.8

[a] Only women ≥50 yr are included.

TABLE 3.—*Distribution by number of births and duration of nursing among parous patients and controls*

Factor[a]	No. of patients	No. of controls	RR	Adjusted RR
No. of births				
1	50	30	1.0	1.0[b]
2	109	75	.8	.8
3	77	88	.5	.5
4	51	70	.3	.4
≥5	63	87	.3	.5
Duration of nursing, mo[c]				
Never	34	18	1.0	1.0[d]
≤36	137	109	.7	.8
37–72	98	115	.5	.8
73–108	42	53	.4	.8
≥109	29	45	.3	.7

[a] Pairs in which either the patient or the control was nulliparous were excluded from the analysis. There were 350 pairs of parous women.

[b] Value was adjusted for AFB.

[c] Total does not add to 350 due to missing values.

[d] Value was adjusted for No. of births.

Elevated risks in nulliparous compared with parous women were also observed in the 14- to 16-year and over-17 categories of menarcheal age, for whom the RR estimates were relatively stable. We did not have adequate data to evaluate the risk associated with nulliparity and menstruation at age 13 or younger; only 2 patients and 2 controls were in that cell. Decreasing age at menarche was associated with increasing risk of breast cancer regardless of AFB. Of the nulliparous women, those whose age at menarche was between 14 and 16 years had 1.2 times the risk of those who started menstruating later.

The patients were older at menopause than were controls (table 1), and those between 45 and 49 were almost 50% as likely to be menopausal than were controls in the same age group (RR = .6, $P = .12$). Among subjects 50 years or older, the RR for age at menopause at or after age 50 was 2.0 compared with those whose menopause began when they were less than 45 ($P = .05$, linear trend test).

Increased parity was associated with a protective effect on breast cancer risk ($P < .001$; table 3); this association remained significant after adjustment was made for AFB. The apparent protective effect of increased parity was restricted to women with an early AFB (<25). Duration of nursing was also significantly associated with a reduction in breast cancer risk among parous women ($P < .001$; table 3) that was explained by the higher parity among controls.

All the women had similar histories of hormone use and exposure to chest x rays. Fifty-five patients and 53 controls claimed a history of oral contraceptive use. Seventeen patients and 20 controls had used other kinds of hormones; all except 3 patients and 2 controls had taken cortisone.

DISCUSSION

These data confirm the association between age at menarche and risk of breast cancer observed in many populations (*3–5, 7–12*). Among Chinese women in Tianjin, the risk of breast cancer increases 50% for every 2-year decrease in age at menarche over a range of age 13 to 17. In Taiwan, Lin et al. (*4*) observed a 1.7-fold increased risk of breast cancer in Chinese women with an early (≤13 yr) versus a late (≥17 yr) menarche. In Japan, Yuasa and MacMahon (*3*) noted a 30% increased risk of breast cancer for every 2-year decrease in age at menarche from 17 to 13 years. Among women under 32 years in Los Angeles, Pike and co-workers (*10*) observed a twofold increased risk of breast cancer among those with age at menarche before 12 years compared with 13 years or later. In Poland, Staszewski (*5*) reported an RR of 1.9 for age at menarche before 16 years compared with 16 years or later in women under age 45.

Our findings on AFB are similar to those reported by MacMahon and associates (*2*) in their international collaborative study. In a comparison of Chinese women, nulliparous women had a threefold increased risk of breast cancer, and those with an AFB after age 35 had a 3.5-fold risk of that of women with an AFB before age 20.

TABLE 2.—*Breast cancer RR according to levels of age at menarche and AFB*

Age at menarche, yr	AFB, yr					
	≤24	No. of patients/ No. of controls	≥25	No. of patients/ No. of controls	Nulliparous	No. of patients/ No. of controls
≥17	1.0	28/68	2.1	44/52	3.4	14/10
14–16	1.9	112/145	3.8	120/76	4.2	26/15
<13	2.3	24/25	5/0	45/22	2.4	2/2

Surgical menopause is a rare event in China. Even though we did not differentiate between surgical versus natural menopause, the results on menopause for all practical purposes represent those of natural menopause. Based on the information obtained from our controls, we estimated that the chance of a Chinese woman being menopausal before age 40 is 0.8%; the probability of her being menopausal before age 45 is 8.5%. These figures are similar to the proportions of U.S. women who achieve a natural menopause before the same ages (*16*). The median age at menopause of our controls was 49.8 years. In Greece, Trichopoulos et al. (*6*) found a 1.5-fold increased risk of breast cancer in women who had a natural menopause when they were between 50 and 54 years old with those under 45. Lubin and co-workers (*12*) observed a similar elevation in risk (1.9) between late (≥50 yr) versus early (<45 yr) menopause among Canadian women. In Tianjin, we also noted a twofold elevated risk of breast cancer in women who stopped menstruating after age 50 compared with those who stopped before they were 45 years old.

As might be expected from their lower risk of breast cancer, Chinese women differ by varying degrees from U.S. white women in their distribution of the major risk factors. Menarche begins considerably later in Chinese girls than it does for whites in the U.S. Only 3% of our controls began menstruating before they were 13; the average reported age was 15.6 years. Lin et al. (*4*) observed a mean reported age at menarche of 15.1 years in their Chinese controls. Table 4 presents the calculated average ages at menarche (reported age in years plus 0.5) for the Tianjin Chinese birth cohorts (controls only) from 1915 to 1945 and a comparison of corresponding figures for Japanese and U.S. white women (*17*). The average age at menarche has declined in Japan and the U.S., but the change in China has been slight. For the 1940–44 birth cohort, the average age of Chinese girls at menarche was about 3 years older than that of whites and about 1½ years older than the Japanese.

A comparison of the distribution of AFB among birth cohorts of Tianjin Chinese (controls only), Japanese, and U.S. whites is given in table 5. The Chinese birth cohort of 1920–29 is distributed similarly as their U.S. counterparts. Both populations have a higher percentage of nulliparous women and a higher proportion of early first births than does the Japanese cohort. The 1930–39 cohort of Chinese women shows a decline in the proportion of nulliparous women and early first births in the population resulting in a distribution that more closely resembles the experience of the Japanese cohort. One explanation for the relatively high percentage of nulliparous women in the Chinese cohort of 1920–29 might be that these women reached their active reproductive years during wartime (Sino-Japanese War between 1937 and 1945 followed by 5 yr of civil war) when many marriages were delayed.

Table 4.—*Average age at menarche (reported age in years plus 0.5) by birth cohort for Chinese, Japanese, and U.S. whites*[a]

Birth cohort	Average age at menarche, yr		
	China	Japan	U.S.
1915–19	16.4	15.6	13.7
1920–24	15.7	15.3	13.4
1925–29	16.3	15.2	13.3
1930–34	16.1	15.5	13.2
1935–39	16.3	14.9	13.2
1940–44	16.0	14.4	13.1
1945–49	16.0	—	—

[a] Data on Japanese and U.S. white women are from (*16*). *Dashes* indicate no data are available.

Table 5.—*Percentage distribution of AFB in certain birth cohorts of Chinese, Japanese, and U.S. whites*[a]

AFB, yr	Chinese		Japanese	U.S.
	1920–29	1930–39	1925–29	1925–29
≤19	19.9	11.8	2.7	20.6
20–24	42.5	48.7	56.2	45.1
25–29	17.8	26.7	26.4	18.3
30–34	7.5	7.2	7.0	5.0
≥35	2.0	2.5	2.2	1.6
Nulliparous	10.3	3.1	5.5	9.4

[a] Data on Japanese and U.S. white women are from (*16*).

Chinese, Japanese, and U.S. white women are similar in their median ages of natural menopause (*17*). However, the proportions of women who experienced surgical menopause are different among the 3 populations. About 30% of U.S. whites achieved menopause surgically; the proportion is about 10% in Japan (*17*). No data are available for the Chinese, but the general impression is that the proportion would be about 1–2%. Pike et al. (*18*) predicted that the rate of breast cancer in China would remain unchanged in the near future on the basis of the distribution of these 3 major risk factors for breast cancer among Chinese women.

Investigators (*19–22*) have reported an inverse association between parity and risk of breast cancer that cannot be accounted for by AFB. In light of these findings, Kelsey et al. (*11*) reviewed the results of the international study of MacMahon and co-workers (*2*) and noted that "births after the first might have a protective effect, at least in Japan, and that very high parity might be protective in São Paulo." In Tianjin, births after the first seem to have additional protective effect for the subgroup of women who had their first children before age 25. Due to the limitation of our data, we could not evaluate these observations further with respect to other aspects of the women's reproductive histories. More comprehensive information on reproductive history is needed for any study of the possible direct association between parity and risk of breast cancer.

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Colorectal Cancer in Chinese and Chinese-Americans [1, 2]

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ABSTRACT—Rationale and plans are described for a collaborative case-control study of large bowel cancer among Chinese-Americans in Los Angeles and the San Francisco Bay Area and among Chinese in Zhejiang Province, People's Republic of China. A common protocol and questionnaire will be used during personal interviews of approximately 400 Chinese and 300 Chinese-American patients with histologically confirmed adenocarcinoma of the colon or rectum and 2,100 Chinese and Chinese-American controls. Controls will be matched to patients on age, sex, and community of residence. The information requested from subjects will permit testing of hypotheses relating colorectal cancer risk to: dietary factors, including intake of fat (saturated and unsaturated), animal protein, fiber, and vitamins A and E and ascorbic acid; physical activity levels and body mass index; reproductive factors among women; history of bowel disease; and family history of cancer. The information requested of Chinese-American subjects will also permit testing of hypotheses relating cancer risk to such migrant factors as United States versus Chinese nativity, duration of residence in the United States, and Chinese province of ancestry. These factors will be tested for associations with cancers of the colon and rectum separately and with cancers of the large intestine as a whole. We will examine sex and geographic differences in relative risks for etiologic factors, location of tumors within the large bowel, histologic subtype of adenocarcinoma, and frequency of accompanying polyps. — Natl Cancer Inst Monogr 69: 43–46, 1985.

Cancer of the large intestine, a major cause of illness and death in the world, comprised 15% of all newly diagnosed cancers in women and 14% in men in the U.S. in 1980. Evidence from geographic correlations and case–control studies suggests several dietary hypotheses for colon and rectum cancers: 1) a positive association with total and perhaps saturated fat; 2) a protective effect of dietary fiber, and 3) a protective effect of cruciferous vegetables. Diverse results of case–control studies concerning the importance of fat and fiber may be partly due to differences in the degree of precision in the methodology used in the various studies or to dietary homogeneity among some of the populations studied. The possible role of alcohol and low intake of vitamins A and E and ascorbic acid in the induction of colorectal cancer requires further study.

The evidence also indicates increased colon cancer risk associated with inflammatory bowel disease (ulcerative colitis, Crohn's disease), syndromes of familial polyposis of the colon, and a family history of large bowel cancer. Recent data suggest that high levels of physical activity and (among females) high parity and exogenous estrogen intake may protect against this cancer. To examine these hypotheses, we are conducting a collaborative case–control study of large bowel cancer among Chinese-Americans in Los Angeles and the San Francisco Bay Area and among Chinese in Zhejiang Province, People's Republic of China, during the period 1984–87.

RATIONALE

The Chinese populations in the 3 study areas offer several advantages for investigations of the etiology and pathogenesis of large bowel cancer. Although relatively homogeneous in genetic background, they are markedly heterogeneous in life-style. Chinese-Americans in the U.S. today comprise a population richly diversified in socioeconomic status, cultural tastes, dietary preferences, degree of assimilation, and family ancestry (*1*). Whereas within-group variation in these attributes is large, it is exceeded by differences between Chinese living here and their counterparts in the People's Republic of China. Such cultural diversity provides an opportunity for the study of relationships between ways of living and colorectal cancer risk.

Also advantageous is the high population density of Chinese-Americans in Los Angeles and the San Francisco Bay Area. The study population will consist of Chinese-American residents of counties covered by the Los Angeles and San Francisco Bay Area Tumor Registries, an area containing approximately 260,000 of the estimated 322,340 Chinese-Americans in California (1980 census). California accounts for 40% of the total Chinese population in the U.S.

Coupled with the varied life-styles of the study populations is their heterogeneity in large bowel cancer risk. Table 1 shows age-adjusted incidence rates for cancers of the colon and rectum among Chinese in Shanghai, Hong Kong, Singapore, Hawaii, Los Angeles, and the San Francisco Bay Area, and among U.S. whites and blacks. Age-adjusted mortality rates are shown in table 2 (Yung-

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TABLE 1.—*Average annual age-adjusted incidence rates (cases/100,000) for cancers of the colon and rectum, 1973–77*[a, b]

Population	Male			Female			Male:female ratio	
	Colon	Rectum	Colon:rectum ratio	Colon	Rectum	Colon:rectum ratio	Colon	Rectum
Chinese								
Shanghai	7	8	0.9	7	7	1.0	1.0	1.1
Hong Kong	14	11	1.3	11	8	1.4	1.3	1.4
Singapore	14	14	1.0	13	8	1.6	1.1	1.7
Hawaii	29	17	1.7	21	9	2.3	1.4	1.9
San Francisco	28	17	1.7	21	11	1.9	1.3	1.6
Los Angeles	31	14	2.2	23	13	1.8	2.2	1.1
San Francisco natives								
White	32	16	2.0	27	10	2.7	1.2	1.6
Black	28	10	2.8	24	10	2.4	1.2	1.0

[a] Rates are adjusted to the world population (*2*).

[b] Source of data was table 1 of (*3*).

Hua C: Personal communication). Several comparisons are noteworthy: 1) Sex- and site-specific rates among Chinese-Americans are consistently higher than the corresponding rates among Chinese in Shanghai. (The smaller differences in mortality than in incidence may reflect higher case fatality rates in China.) These contrasts are strengthened by the fact that Shanghai colorectal cancer rates are among the highest in China (*4*). The Chinese study areas of Hangzhou and Ningbo are located within 120 miles of Shanghai and have comparable colorectal cancer rates. The contrasts indicate marked heterogeneity in disease risk among the study subjects.

2) Chinese-American rates are comparable to those of native-born whites. This comparability suggests that U.S.–Chinese differences in colorectal cancer risk are largely if not wholly due to differences in life-style or other environmental factors. Data from Hawaii (*5*) indicate no difference in colorectal cancer risk between first- and second-generation Asians. These data suggest that environmental factors alter risk within a relatively short fraction of the human life-span. By contrast, stomach cancer rates among first-generation Japanese migrants tend to resemble rates in Japan, whereas those of second-generation migrants resemble those of their host country (*6*).

3) The male-to-female ratios suggest greater susceptibility or greater exposure to etiologic factors among male than among female Chinese-Americans. These sex differences in acquired colorectal cancer risk are consistent with observations among other migrant groups (*7*). They indicate that useful new clues may result from scrutiny of sex differences in relative risks for dietary and other etiologic factors and in tumor pathology.

4) Although Chinese-American rates for cancers of the colon and rectum exceed those among Chinese in Shanghai, the relative increase is larger for colon than for rectum cancer. The disparity could reflect a different etiology for these 2 cancers, with Chinese-Americans exposed to factors having greater impact on cancer in the colon than in the rectum. Alternatively, the disparity could reflect geographic differences in diagnosis, particularly in site assignment of those cancers occurring in the rectosigmoid junction. To investigate this issue, collaborating pathologists in the 2 countries will develop uniform and standardized criteria for classifying anatomic location of tumor.

Examination of temporal trends in rates of large bowel cancer among Chinese in the study areas is limited by lack of data on cancer incidence rates in the People's Republic of China. The only population-based cancer registry in

TABLE 2.—*Average annual age-adjusted mortality rates (deaths/100,000) for cancers of the colon and rectum, 1973–77*[a]

Population	Male			Female		
	Colon	Rectum	Both sites	Colon	Rectum	Both sites
Chinese						
Urban Shanghai	NA[b]	NA	12	NA	NA	9
Rural Shanghai	NA	NA	11	NA	NA	8
Hawaii	15	2	17	9	2	11
San Francisco	15	6	21	9	3	11
San Francisco natives						
White	13	4	17	10	2	12
Black	11	3	14	11	2	13

[a] Rates are adjusted to the world population (*2*).

[b] Rates are not available.

China is the Shanghai Tumor Registry, which was established in 1958 to serve the metropolitan area of Shanghai, now estimated to have a population of 11 million. Incidence data for 1958 and 1975 indicate that colon cancer rates have remained stable or decreased over this period, whereas those for cancer of the rectum have increased (*8*).

Age-adjusted incidence rates for cancers of the colon and rectum combined among Chinese-Americans in Hawaii have almost doubled from 1960 to 1978 (*9*). These trends are consistent with those among whites in Connecticut; incidence rates for colon cancer have risen for both sexes over the past three decades, but those for cancer of the rectum have remained constant (*10*).

These trend differences between Chinese and Chinese-Americans suggest that 1) the 2 populations are exposed to different etiologic factors, and 2) useful information will result from scrutiny of intercountry differences in relative risks for dietary and other etiologic factors.

PLANNING

The collaborative project now under way is the result of discussions and joint planning that began in 1982 when Stanford's Northeast Asia Forum offered to help the U.S. team to arrange a collaborative project with counterparts in China. It was decided that such a project must address important scientific questions that could not be examined except through close collaboration with specialists in China. The tentative choice of the research topic and considerable enthusiasm for the project emerged from discussions among members of the U.S. team. Chinese specialists, under the leadership of Dr. Bing Li, Deputy Director of the Cancer Institute, Chinese Academy of Medical Sciences, joined the planning process immediately after the choice of a tentative research topic.

Interest focused on the study of colorectal cancers because these neoplasms constitute a major public health problem in both countries. Because Zhejiang Province, located in East Central China, experiences the highest colorectal cancer mortality rates in the country (*4*), and Zhejiang Medical University in Hangzhou is the national center for research on large bowel cancers, officials of the Zhejiang Provincial Bureau of Public Health and the Medical University were asked by Dr. Bing Li to take responsibility for the proposed joint study. These specialists (including Dr. Yu Shangchen, from the Provincial Bureau of Public Health, and Dr. Jiwu Wang, President of Zhejiang Medical University) helped to define the project in a series of meetings with representatives from Stanford University and the University of Southern California. These exploratory meetings laid the groundwork for the joint planning of study hypotheses, design, protocol, and analyses; final details of the project evolved in a meeting at Stanford University in October 1982.

The details of the proposed study were explored with specialists in and from China, and the Northeast Asia–U.S. Forum staff played an essential facilitating role. Their familiarity with policies and procedures in the U.S. and China and experience in arranging other collaborative projects enabled Forum staff to anticipate, recognize, and help resolve problems that arose in the course of negotiations between the American and Chinese teams. One of us (T.F.) met with colleagues in China three times during the planning period and 2 Chinese (Z.S. and B.J.L) visited the United States at a crucial stage in the discussions. Dr. Henderson spent 3 months in China during the planning phase. Although the components of the study involve a unified protocol and analysis, investigators responsible for each component obtained funds separately from their governments.

STUDIES IN ZHEJIANG PROVINCE

Two population-based colorectal cancer screening programs were conducted in Haining County during the periods 1977–78 (*11*) and 1980–81. A total of 257,132 adults aged 30 or more years were screened, with response rates of 87 and 64% for the 2 periods, respectively. Screening included physical examination, medical history, rectal examination, occult blood test and, if warranted, biopsy, polypectomy, or rectoscopy. Table 3 shows the resulting prevalence rates for disorders of the large bowel.

The geographic distribution of death rates for colorectal cancer in China correlates positively with the distribution of prevalence rates for schistosomiasis (*Schistosoma japonica*). However, screening did not demonstrate differences in prevalence of polyps or adenomas containing *Schistosoma* ova among those with and without colorectal cancers.

Investigators at Zhejiang Medical University also conducted a case–control study of colorectal cancer in Haining County in 1983. A structured questionnaire concerning medical and environmental factors was administered in personal interviews with 97 newly diagnosed patients with cancers of the colon or rectum, 97 control patients hospitalized with cancers at sites other than the gastrointestinal tract, and 194 neighborhood controls. Controls were matched to patients on sex and age (within 5-yr intervals).

Elevated relative risks were associated with a history of gastrointestinal polyps, drinking water obtained from pools or ditches, and with long-term contact with livestock in and around the home. The study did not include questions concerning diet.

TABLE 3.—*Prevalence rates of large bowel disorders in Haining County, Zhejiang Province*

Yr of screening	No. screened	Response rate, %	Prevalence rates/100,000[a]		
			Adenocarcinoma	Polyps	Intestinal ulcer
1977–78	198,950	87.0	32 (19)	1,660 (3,053)	81 (172)
1980–81	58,182	64.3	38 (10)	2,350 (1,368)	85 (50)

[a] *Numbers in parentheses* are No. of cases.

OBJECTIVES AND DESIGN OF THE UNITED STATES-CHINESE STUDY

The major factors to be tested for their relationship to the etiology of adenocarcinoma of the colon, rectum, and large intestine as a whole are listed in table 4. We will examine sex and geographic differences in 1) etiologic roles played by these characteristics, 2) location of tumors within the large bowel, 3) histologic subtype of tumors, and 4) frequency of accompanying polyps and adenomas. In particular, we will evaluate such variability among Chinese-Americans and Chinese living in high- and low-risk areas of China. Comparison of data collected in this study with 1973-77 Surveillance, Epidemiology, and End Results Program cancer incidence data for the San Francisco Bay Area (*12*) and those from the Los Angeles Tumor Registry will permit evaluation of differences in factors 1-4 between Chinese-Americans and native Caucasians.

To ensure comparability of study design and analysis in the 2 countries, scientists at Zhejiang Medical University will work with investigators at Stanford University and the University of Southern California throughout the 4-year study period. Investigators in the U.S. will visit Zhejiang Medical University annually. Study protocol will be standardized according to the following steps:

1) Pathologists will develop a common convention for classifying tumor location and histologic type; 2) physicians at the 3 institutions will use common procedures to identify patients and controls; 3) the questionnaire will contain a core of questions common to both countries, as well as questions special to the needs of each country; 4) nutritionists will develop a common set of instructions for interviewers regarding use of the questionnaire and food models; 5) nutritionists will develop common conventions for the classification of nutrient intake data; 6) project managers will instruct participating clerks, coders, and keypunchers on common procedures for data storage, and all data amassed at all 4 sites will be available for analysis by the 3 institutions; 7) biostatisticians will agree upon common statistical analyses; and 8) all participating epidemiologists and biostatisticians will confer on the interpretation and presentation of statistical data and study results.

Both groups hope that this and other U.S.-Chinese collaborative projects in cancer epidemiology will mark the beginning of productive and fruitful cooperation in reducing mortality and morbidity from neoplastic disease.

TABLE 4.—*Factors to be examined for relationship to large bowel cancer risk*

- Diet
  - Increased fat intake (animal or plant, or both, saturated or unsaturated)
  - Increased animal protein intake
  - Low fiber intake
  - Low intake of vitamins A, E, and ascorbic acid
  - Decreased green, leafy, or cruciferous vegetable intake
  - Decreased fruit intake
  - Increased alcohol intake
- Low physical activity levels of work and leisure
- Obesity
- Reproductive and catamenial factors among females
- Site-specific familial cancer occurrence
- Inflammatory bowel disease
- Degree of westernization (U.S. only)
  - U.S. nativity (Idai, Erdai, Sandai)
  - Duration of U.S. residence
  - Timing of dietary and other cultural changes
  - Chinese province of ancestry
- History of schistosomiasis (China only)

ADDENDUM

Subsequent to the Symposium, this case-control study was expanded to include Chinese colorectal cancer patients and controls living in Vancouver, British Columbia, under the direction of Mr. Richard P. Gallagher.

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Risk Factors for Hepatocellular Carcinoma in Guangxi, People's Republic of China [1]

Fu-Sun Yeh, Chih-Chun Mo, *and* Rui-Chi Yen [2, 3, 4]

ABSTRACT—Fusui County in the Guangxi Autonomous Region of China is a high-risk area for hepatocellular carcinoma (HCC). In 1971–73, the average annual standardized (world population) mortality rate of HCC in Fusui was 20.09 and 111.75/100,000 person-years for females and males, respectively. Epidemiologic and pathologic studies of HCC have been conducted in Fusui since 1959. This paper describes some of the studies relating to the hepatitis B virus infection and aflatoxin contamination of foodstuffs. — Natl Cancer Inst Monogr 69: 47–48, 1985.

The average annual adjusted (1964 Chinese population) mortality rate of HCC in Guangxi between 1971 and 1973 was 16.49/100,000. In some areas of Guangxi, HCC accounted for 57 and 70% of all cancer deaths in females and males, respectively (*1*). The highest rates occurred in Fusui County where the average annual standardized (world population) mortality rate in 1971–73 was 20.09 and 111.75/100,000 for females and males, respectively.

The marked geographic distribution of HCC in China (*2*) suggests that environment plays an important role in the causation of this disease. Epidemiologic and pathologic studies have been conducted in Guangxi since 1959 with emphasis on field studies in Fusui County. Studies on the 2 most important risk factors for HCC in Guangxi, HBV infection and aflatoxin contamination of foodstuffs, are described in this paper.

HEPATITIS B VIRUS INFECTION

We (Yeh FS, Mo CC, Luo S, et al: Unpublished observations) recently completed a collaborative case–control study of HCC with colleagues at the University of Southern California Comprehensive Cancer Center. Sera from 50 HCC patients in Guangxi and 50 age- and sex-matched hospital controls were tested for HBV markers by radioimmunoassay. Table 1 shows 43 patients versus 11 controls to be HBsAg positive at the time of hospitalization (RR = 17.0, 95% confidence limits = 4.3, 99.4).

As part of a nationwide multicenter study, autopsy and biopsy specimens of liver tissues from patients with HCC, those with cirrhosis, and controls in Guangxi were examined histochemically for HBsAg with the use of Shikata's stain (*3*). A comparison of the results for patients from Guangxi and nationally is given in table 2. Yen et al. found that 70.4% of HCC patients in Guangxi were positive for HBsAg compared with 6.3% of the nonhepatic controls.

In a serologic survey of HBV markers among inhabitants of Fusui County conducted in 1974–77, the investigators (*4*) used the method of reverse passive hemagglutination to determine HBsAg positivity. Five hundred fifty-one HBsAg-positive subjects and an equal number of age- (within 5 yr) and sex-matched HBsAg-negative subjects were selected from survey participants and were followed up to 1982. Total years of follow-up ranged from 5 to 8. Fourteen HCC developed among HBsAg-positive subjects; the mortality rate was 25.4/1,000 person-years compared with 3.6/1,000 in the HBsAg-negative group (RR=7.1, $P < .01$).

AFLATOXIN CONTAMINATION OF FOODSTUFFS

In Fusui County, peanut, peanut oil, corn, and beans were found to be markedly susceptible to aflatoxin B_1 contamination. Among these foods, corn is most commonly eaten and is considered a staple in many parts of the county. Samples of these foods were collected from families in different villages throughout the county. On the basis of the determined aflatoxin B_1 content of these foods and the amounts consumed by the inhabitants of each village, we computed an estimated annual intake per person for each village. The villages were then grouped into "light" versus "heavy" contamination areas. Average annual intake per person in the heavily contaminated villages was 6.016 compared with 0.638 mg in lightly contaminated villages. Table 3 shows that the mortality rate of HCC among HBsAg-positive individuals in the heavily contaminated areas was 9.85 times higher than that in those in lightly contaminated areas (*4*). Among HBsAg-negative individuals residing in areas heavily contaminated with aflatoxin, 2 developed HCC. One cannot rule out the possibility that these 2 patients were misclassified as

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ABBREVIATIONS: HCC=hepatocellular carcinoma(s); HBV=hepatitis B virus; HBsAG=hepatitis B surface antigen(s); RR=relative risk(s).

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[3] We thank the staff of the Liver Cancer Institute of Fusui County who collaborated with us in the research conducted for this study.

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TABLE 1.—*Prevalence of HBV markers in HCC patients and controls*

HBV marker	Patients		Controls	
	No.	Percent	No.	Percent
HBsAg positive[a]	43	86	11	22
Anti-HBs positive alone	0	0	4	8
Anti-HBc positive alone (low titer)	0	0	1	2
Both anti-HBs and anti-HBc positive	6	12	27	55
All markers negative	1	2	6	12
Total	50	100	49[b]	99[c]

[a] Matched odds ratio = 17.0; 95% confidence limits = 4.3, 99.4.

[b] No plasma was available from a control who has HBsAg-negative to test for anti-HBs and anti-HBc (hepatitis B core antigen).

[c] Percentages do not add to 100 due to rounding error.

HBsAg-positive because of the insensitive nature of the test used.

During 1965–74, we (*5*) conducted 2 experiments in which rats were fed foods from Fusui County believed to be contaminated with aflatoxin B_1 and found that among the 96 rats fed contaminated foods, 34 developed HCC, whereas 24 control rats did not.

Investigators working in the Tumor Research Laboratory of Guangxi Medical College (*6*) examined domestic animals in Fusui County during 1964–74 and found that 3 of 46 ducks and 3 of 160 dogs had HCC, but only 2 of 1,388 chickens had it.

TABLE 2.—*HBsAG* (*Shikata's stain*) *positivity rates in liver tissue specimens from patients with different diseases*

Disease	Guangxi		China	
	No. positive/ No. tested	Percent	No. positive/ No. tested	Percent
HCC	100/142	70.4	401/500	80.2
Cirrhosis	55/99	55.6	580/757	76.6
Other malignant tumors	2/40	5.0	6/141	4.3
Nonhepatic, nonmalignant diseases	2/32	6.3	4/81	4.9

TABLE 3.—*Mortality from HCC by HBsAg status in areas of Fusui County with varying degrees of food contamination by aflatoxin, 1974–82*

Aflatoxin contamination	HBsAG status	Cumulative person-yr	HCC	
			No. of deaths	Rate
Heavy	Positive	2,002	13	649.35
	Negative	2,029	2	98.57
Light	Positive	1,517	1	65.92
	Negative	1,531	0	0.00

CONCLUSIONS

Our studies indicate that HBV infection is a major risk factor for HCC in Guangxi. Exposure to aflatoxin-contaminated foods is another in some parts of this region. The presence of both factors may explain the unusually high incidence of HCC in Fusui County.

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Some Epidemiologic Observations of Nasopharyngeal Carcinoma in Guangdong, People's Republic of China [1, 2]

Chen-Chuan Li, [3] Mimi C. Yu, [4] *and* Brian E. Henderson [4]

ABSTRACT—Chinese in the province of Guangdong have the highest risk of nasopharyngeal carcinoma (NPC) in China. Within Guangdong, variation in rates among the 3 major dialect groups is threefold. The Cantonese who reside in the central region of Guangdong display the highest risk of NPC. Among the Cantonese, those living on boats have twice the risk of those who live on land. These observations are consistent with earlier studies of southern Chinese residing in Hong Kong and Southeast Asia. — Natl Cancer Inst Monogr 69: 49–52, 1985.

Although NPC is rarely seen in most parts of the world (*1*), it is common among Chinese residing in the southeastern region of China. Table 1 lists the 6 provinces or autonomous regions in China with age-standardized (world population) mortality rates of NPC exceeding that of the national rate (*2*). Figure 1 shows that these high-risk provinces form a contiguous region covering the southeastern corner of the country. The coastal Province of Guangdong, which borders 4 of the other 5 high-risk provinces, has the highest mortality rate of NPC: The age-standardized mortality rate among males was 3.7 times the national rate. The provincial rate among females was 2.8 times the national rate.

RELATIVE FREQUENCIES

In 1964–82, the Tumor Hospital of Chungshan Medical College[5] in the City of Guangzhou registered 159,390 cases of cancer. The site most frequently registered was the nasopharynx, i.e., 32.1% (table 2). These NPC cases constitute 77.7% of all head and neck tumors registered at the hospital (table 3). Over the 19-year period, these proportions remained relatively unchanged.

MORTALITY RATES

According to a survey conducted in Guangdong during 1970–72, the annual age-adjusted (1964 Chinese population) mortality rates of NPC in females and males were 3.8 and 9.9 per 100,000 population, respectively. Table 4 shows the mortality rates of NPC by the 9 districts of Guangdong (fig. 2). The male preponderance persisted throughout the province. Mortality rates of NPC in the central districts of Guangdong (the Pearl River Delta region), which are Shaoching, Foshan, and Guangzhou, were more than twice the rates in Swatow (also called Chiu Chau or Teochow) and Meihsien districts to the northeast. The survey also revealed that the mortality rates of NPC among boat people (those who live on boats parked along the banks of the Pearl River Delta and who are either fishermen or sea transporters) were especially high. The age-adjusted mortality rate in males was 31.6/100,000.

INCIDENCE RATES

In 1970, a population-based cancer registry was established in the Chungshan County of Foshan District. Between 1970 and 1979, the annual age-adjusted (1964 Chinese population) incidence rates for males averaged 20.5/100,000 and were about 2.5 times higher than in females (table 5). The rates were approximately the same over the entire 10-year period.

ANALYTICAL EPIDEMIOLOGY

Hu and Huang (*3*), who conducted a case–control study of NPC in Guangzhou during 1964–65, studied patients whose cases were histologically confirmed at the Tumor Hospital of Chungshan Medical College. Their patients had been exposed to chemical fumes and other nasal irritants. Controls were selected from noncancer patients seen at the Ophthalmology and Surgery Clinics of the First and the Second Affiliated Hospitals of Chungshan Medical College; surgical patients with gastrointestinal, respiratory, or endocrine conditions were excluded. The controls were individually matched to the patients on sex, age (within 5 yr), and neighborhood of residence. Hu and Huang found that NPC was significantly associated with the following attributes (table 6): Patients had an ethnic origin in Guangdong (RR = 5.4), usually worked as chefs or in restaurant service (RR = 10.4), smoked 21 or more cigarettes/day (RR = 1.9), or had histories of pulmonary tuberculosis (RR = 2.9).

ABBREVIATIONS: NPC=nasopharyngeal carcinoma; RR=relative risk(s).

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TABLE 1.—*Age-standardized (world population) annual mortality rates of NPC in high-risk provinces, 1973–75*

Province/ autonomous region	Males		Females	
	Rate	RR	Rate	RR
Guangdong	12.5	3.7	5.0	2.8
Guangxi	8.5	2.5	3.5	1.9
Fujian	6.1	1.8	2.9	1.6
Hunan	5.6	1.7	3.0	1.7
Jiangxi	4.2	1.2	2.0	1.1
Zhejiang	4.1	1.2	1.9	1.1
China	3.4	1.0	1.8	1.0

TABLE 2.—*Percentages of common cancers among all cancers registered at the Tumor Hospital, Chungshan Medical College, 1964–82*

Site/type	No. of cases	Percent
Nasopharynx	51,103	32.1
Liver	19,756	12.4
Lung	16,452	10.3
Esophagus	9,527	6.0
Breast	8,015	5.0
Cervix	7,720	4.8
Rectum and colon	4,738	3.0
Stomach	4,599	2.9
Lymphoma	4,147	2.6
Others	33,333	20.9
Total	159,390	100.0

TABLE 3.—*Percentages of common cancers among cancers of the head and neck registered at the Tumor Hospital, Chungshan Medical College, 1964–82*

Sites	No. of cases	Percent
Nasopharynx	51,103	77.7
Larynx	2,436	3.7
Thyroid	2,002	3.0
Salivary gland	1,843	2.8
Tongue	1,586	2.4
Maxillary sinus	1,099	1.7
Others	5,717	8.7
Total	65,786	100.0

RECENT PROGRESS

Mortality and incidence data collected since the early 1970s confirm earlier observations based on a hospital series that NPC is a common cancer in the Province of Guangdong. The rates of NPC over the past decade in Zhongshan City have remained about the same; Ho (*4–6*) observed similarly stable rates of NPC in Hong Kong since the inception of a cancer registry there in 1965. Ho pointed out that autopsy reports showed NPC to have been prevalent in Guangdong for at least 60 years (*7, 8*),

TABLE 4.—*Average annual age-adjusted (1964 Chinese population) mortality rates of NPC by districts in Guangdong*

Districts	Male	Female	Male:female
Shaoching	16.0	5.8	2.8
Foshan	14.2	5.7	2.5
Guangzhou	12.1	4.3	2.8
Huiyang	10.6	3.8	2.8
Shaokuan	8.9	3.6	2.5
Chanjiang	7.5	3.1	2.4
Hainan	8.0	2.6	3.1
Swatow (Chiu Chau)	6.2	2.9	2.1
Meihsien	5.3	2.0	2.7
Guangdong	9.9	3.8	2.6

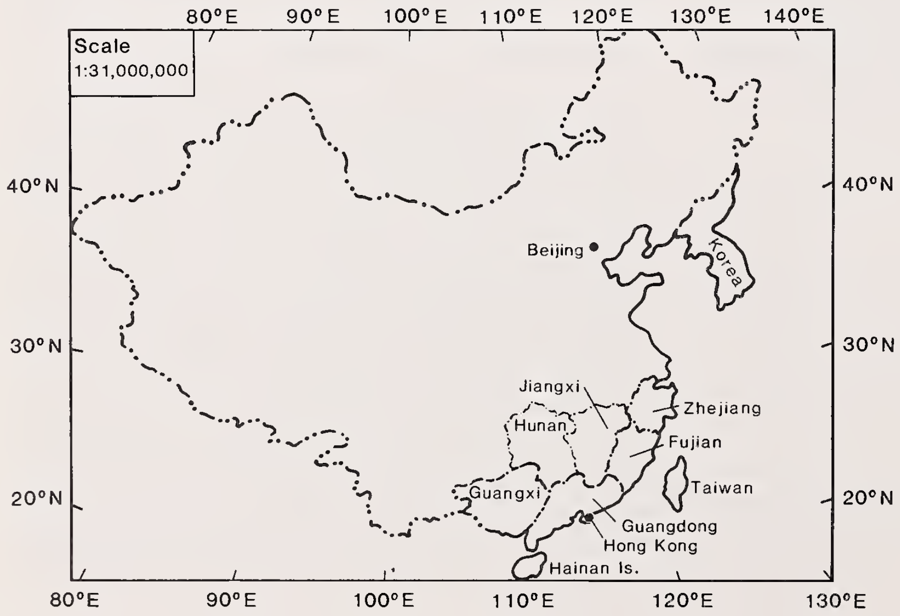

FIGURE 1.—Map of the People's Republic of China.

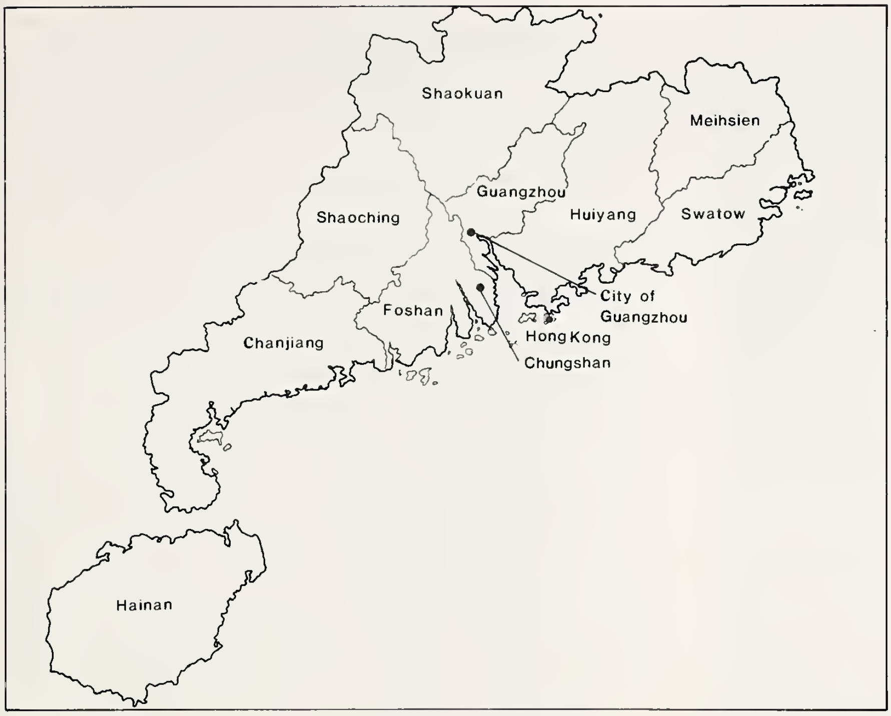

FIGURE 2.—Province of Guangdong.

and thus the disease is not likely to be linked to modern environmental hazards.

A comparison of mortality rates of NPC by administrative districts in Guangdong reveals that the rates vary threefold among males within the Province, ranging from a low of 5.3 in Meihsien to a high of 16.0/100,000 in Shaoching. The geographic variation in the mortality of NPC within Guangdong closely parallels the distribution of dialect groups within the Province. The Guangzhou, Shaoching, and Foshan Districts (Pearl River Delta Region) are inhabited mostly by the Cantonese who form the largest dialect group in the Province. The Meihsien District is inhabited mostly by the Hakkas who originated in northern China[6] and migrated to Guangdong about 700 years ago during a major civil war. The Swatow District is inhabited by the Chiu-Chauese who are culturally close to the Fukienese in the neighboring Province of Fujian. These 3 dialect groups are distinct from each other, not only in their dialects, but also in their cultures. In comparison, the Cantonese have the highest risk of NPC, the Hakkas have the lowest, whereas the Chiu-Chauese display a risk intermediate between the other 2 dialect groups. Such observations are consistent with studies of dialect group variations in Chinese in Hong Kong, Singapore, and Malaysia (*9–11*); Cantonese had the highest risk of NPC among the 3 dialect groups. Relative to the Cantonese in Singapore, the Chiu-Chauese and the Hakkas in Singapore displayed a reduction in risk of NPC of about 30 and 60%, respectively (*9*). In Malaysia, the incidence

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[6] Hakkas originated chiefly in Honan Province.

TABLE 5.—*Average annual age-adjusted (1964 Chinese population) incidence rate of NPC in Chungshan County*

Yr	Male	Female	Male:female
1970	18.4	9.3	2.0
1971	25.8	10.1	2.6
1972	21.5	11.1	1.9
1973	18.8	9.8	1.9
1974	21.7	8.9	2.4
1975	18.8	11.2	1.7
1976	20.1	9.6	2.1
1977	19.0	8.2	2.3
1978	20.2	8.7	2.3
1979	21.3	9.0	2.4
1970–79	20.5	8.3	2.5

TABLE 6.—*Risk factors for NPC in Guangdong*[a]

Factor	No. of cases	No. of controls	Crude RR
Ethnic origin			
Guangdong	209	193	5.4
Other	4	20	1.0
Usual occupation			
Chef/restaurant service	10	1	10.4
Other	203	212	1.0
Cigarette smoking			
Light smoker or nonsmoker	149	174	1.0
≥21 cigarettes/day	64	39	1.9
History of pulmonary tuberculosis			
No	182	201	1.0
Yes	31	12	2.9

[a] *See* (*3*).

rates of NPC in Hakkas were 40–50% those of the Cantonese (*10*). In Hong Kong, the risk of NPC among Chiu-Chauese was 60–70% that of the Cantonese (*11*).

A comparison of NPC mortality between the people who live on boats parked along the banks of the Pearl River Delta and land dwellers in the same region reveals that the boat people have a twofold increased risk of NPC compared with the land population. This confirms the observation of Ho (*12*) in Hong Kong where the incidence rate of NPC in boat people also is about two times that of land dwellers. Ho (*13*) argued against exposure to inhalants as a major risk factor for NPC in Chinese by stressing the high risk of NPC among these boat people who cook in the open and are not exposed to indoor pollutants. His observation that these people eat a large quantity of salted fish was important in his formulation of the hypothesis that consumption of salted fish, especially in early childhood, is a risk factor for NPC in Chinese (*12*). Four case–control studies that were conducted with southern Chinese populations and tested Ho's hypothesis (*14–17*) showed a positive association between salted fish intake and NPC. The most convincing evidence came from the latest study in Hong Kong, the results of which are reported in this monograph (*17*). The study estimates that 80% of NPC in Hong Kong can be attributed to salted fish consumption at an early age.

In light of the recent findings (*14–17*) that suggest salted fish consumption is a factor in the etiology of NPC in Chinese, we initiated a case–control study in Guangzhou, Guangdong, aimed at investigating the relationship between lifetime dietary patterns and NPC. The study identifies incident cases of NPC among Guangzhou residents through the Tumor Hospital of Chungshan Medical College. Individually matched (on sex and age within 5 yr) neighborhood controls serve as the comparison group.

Another test of Ho's hypothesis is a comparison of the consumption pattern of salted fish between the Cantonese, the Hakkas, and the Chiu-Chauese. Ho predicts a higher consumption of salted fish, especially in early childhood, among the Cantonese relative to the Hakkas and the Chiu-Chauese. Planning for such a dietary survey is under way.

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Air Pollution and Lung Cancer in Liaoning Province, People's Republic of China [1]

Han-Pin Xiao [2] *and* Zhao-Yi Xu [3, 4, 5]

ABSTRACT—A correlation study linking age-adjusted lung cancer mortality rates with indices of air pollution was conducted as a first step in the investigation of the high rate of lung cancer in Liaoning Province. Mortality rates for this cancer during 1976–78 for males and females were elevated in the large industrial cities with metallurgical processing and machinery manufacturing industries, after smoking was taken into account. However, there was little correlation between measures of total suspended particulates and lung cancer rates across the 10 major cities of the Province. Neighborhood air pollution indices correlated significantly with local commune mortality rates within the largest city, and lung cancer rates were higher near certain point sources of industrial pollution (including a copper-zinc smelter). These findings indicate that the atmospheric pollution in this northern Chinese province may contribute to lung cancer risk and that further analytic epidemiologic study in this high-risk area is warranted for evaluation of the role of outdoor and indoor air pollutants. — Natl Cancer Inst Monogr 69: 53–58, 1985.

There is general agreement that heavy exposure to specific contaminants in the air (such as asbestos, inorganic arsenic, coke oven emissions) increases the risk of lung cancer. However, the contribution of air pollution to the etiology of lung cancer has not been confirmed. Most epidemiologists hold the view that air pollution plays a minor role in the risk of lung cancer in urban areas.

In China, air pollution is severe in residential areas, due to the proximity of industries and the fact that the country depends on coal as its primary source of energy. The possibility of a substantial risk to health from air pollution became evident when we examined the findings of the 1973–75 cancer survey conducted in China. Liaoning Province, which is a heavily industrial area, had the highest lung cancer mortality among the provinces. Rates in large cities (Shenyang, Luda) of the Province were exceeded only by the rate in Shanghai. To help evaluate the role of air pollution, the staff of the PHAE Station of Liaoning Province, in collaboration with the 10 municipal PHAE Stations, conducted a correlation study to provide leads to understanding the relationship of air pollution, smoking, and occupation in the development of lung cancer.

MATERIALS AND METHODS

All deaths attributed to lung cancer during 1976–78 among residents of 10 Liaoning cities were identified by methods identical to those used in the 1973–75 national mortality survey. We visited the offices of all neighborhood committees, where rosters of the local neighborhood population are kept and vital events recorded, so that deaths and causes of death occurring during 1976–78 could be ascertained. Cause of death was then confirmed by review of available records at local clinics and higher level medical facilities, and by interviews with physicians, other medical practitioners, and relatives of the deceased regarding the death. Age-adjusted lung cancer mortality rates for males and females were calculated for each city. The 1964 Chinese population and the 1960 U.S. population (for comparison with age-adjusted rates in the U.S.) were used as standards.

We (personnel of the PHAE Stations) sought interviews in the homes of relatives of all persons who died of lung cancer. We used a uniform questionnaire to record histories of smoking, residence, and occupation and of occupational exposures to the following potential carcinogens: pitch tar compounds, asbestos, nickel, chromium, arsenic, beryllium, cadmium, lead, zinc, wood dust, nitrosamines, radiation, and mustard gas.

To have comparable smoking data from the general population of the 10 cities, we randomly selected 2 streets from each city and asked all residents to fill out a questionnaire on smoking habits. A neighborhood committee delivered and collected the questionnaires from the participants.

To measure the level of air pollution, we set up 3 to 5 sites in each city, except Anshan, which had 8. These sites were chosen from zones within the city with distinctly different mortality rate levels. Each site was located in a residential area within the zone about 2–4 m above ground and had to be at least 25 m away from any domestic chimney. The air quality was monitored continuously for 5 days each January and July during 1980–82. Measurements were obtained on TSP, SO_2, and BP.

We used a linear regression model to analyze the correlations between age-adjusted mortality rates for the 10 cities and smoking habits, occupation, and levels of air pollution.

ABBREVIATIONS: PHAE=Public Health and Anti-Epidemic Station (Liaoning Province); TSP=total suspended particulate matter; SO_2=sulfur dioxide; BP=benzo[*a*]pyrene; *r*=coefficient of correlation.

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In addition, we used data on TSP and falling dust monitored at 7 and 12 sites in 1972–73 and 1955–57, respectively, in Shenyang. We compared these data with the age-adjusted mortality rates for the local communes where the monitoring sites were located. Finally, we calculated the lung cancer mortality rate for the 17,000 people living in Guongming Street located within 2 km and downwind of a large nonferrous (copper–zinc) smelter. The observed cases of lung cancer were then compared with the expected, with Shenyang mortality rates used as a standard.

RESULTS

A total of 2,896 deaths due to lung cancer were recorded for the period 1976–78 in the 10 Liaoning cities. Age-adjusted lung cancer mortality rates for the cities are shown in table 1. We classified the 10 cities into 5 categories by level of mortality rates. Group 1 (Shenyang and Anshan), where metallurgical processing and machinery production are the main industries, had the highest rates. Group 2, which included 3 cities with petrochemical industries, ranked second. All these 5 cities have large populations, i.e., from 450,000 to 2,000,000. The smaller cities, which had light industry (e.g., textile manufacturing), had lower mortality rates (group 4). Yinkou (in group 3) has a shipbuilding plant in addition to light industry; its mortality rate was between those of groups 2 and 4. The lowest rate was seen in Fuxin (in group 5), which has a coal-burning power station located in the center of the city.

Table 2 presents a comparison of the age-adjusted mortality rates (adjusted to 1960 U.S. population) for 1976–78 in 10 cities with the 1970–75 rates for U.S. whites (*2*). The rates for Chinese males were less than two-thirds those for U.S. white males, but rates for females for some cities were much higher than those for U.S. white females (e.g., rates in Shenyang, Anshan, and Yinkou were double the U.S. rates). The male-to-female ratios were only 1.7:1 and 1.4:1 for Shenyang and Anshan, respectively, and around 2:1 in the remaining cities; these are much lower than the male-to-female ratios for Europe and the U.S., which are about 4:1 to 6:1 (*3*).

TABLE 2.—*Lung cancer mortality rates (age-adjusted to 1960 U.S. Standard Population) for 10 Chinese cities and for U.S. whites (1970–75) by sex*

City	Males	Females	Male-to-female ratio
Shenyang	41.9	25.1	1.67
Anshan	39.2	27.3	1.44
Luda	42.3	21.3	1.99
Jinzhou	33.5	16.7	2.00
Fushun	32.8	16.2	2.02
Yinkou	21.5	24.9	0.86
Dandong	22.5	13.7	1.64
Liaoyang	28.2	11.5	2.45
Chaoyang	20.8	4.5	4.62
Fuxin	18.3	8.2	2.23
U.S. whites	58.6	12.8	4.58

We used data from the interviews to evaluate the influence of cigarette smoking on the city differences. Members of households of the persons who died of lung cancer were interviewed. A nearly as high participation rate was obtained for the population sample. As shown in table 3, the differences in the percentage of smokers among persons over 20 years old in the general population of the 10 cities were small. They ranged from 34.6 to 45.9% with an average of 39.7% (62.6% for males and 15.4% for females). Among the patients with lung cancer, the percentages ranged from 70.1 to 85.1, with an average of 77.2 (85.5% for males and 62.3% for females). Thus smoking is clearly related to lung cancer risk in both sexes. However, a large proportion of these females were nonsmokers. Because 1) our study population sample is thought to be representative of the total population and 2) the smoking status of each participant is known, we can estimate the size of the nonsmoker population in each city and therefore estimate the lung cancer mortality rates for nonsmokers. The mortality rates among nonsmokers differed greatly among cities (table 4). Among females, the rates for Shenyang, Anshan, and Luda (cities 1, 2, and 3) still headed the list, and their rates were several times higher than those for the other cities. The findings were similar among males, except the rates for Anshan were not particularly high.

Air pollution in these 10 cities was observed to be severe (table 5). All values of the indices exceeded the Chinese standard of acceptable air quality, especially in January. Values of TSP were two to four times the standard, and those for BP were from 33 to over 100 times higher than the

TABLE 1.—*Lung cancer mortality rates (1/100,000) and characteristics of the 10 cities during 1976–78*

Category	City	Population	Main industry	No. of cases	Mortality rates
1	Shenyang	2,000,000	Machinery and metallurgical processing	1,218	17.7
	Anshan	700,000	″ ″ ″ ″	318	17.6
2	Luda[a]	1,000,000	Petroleum and chemical factories	533	15.9
	Jinzhou	450,000	″ ″ ″ ″	144	14.2
	Fushun	900,000	″ ″ ″ ″	357	14.6
3	Yinkou[a]	250,000	Light industry	91	12.4
4	Dandong	300,000	″ ″	97	10.4
	Liaoyang	200,000	″ ″	49	10.3
	Chaoyang	120,000	″ ″	22	7.6
5	Fuxin	400,000	Coal mine and power station	67	7.4

[a] This city also has shipbuilding factories.

TABLE 3.—*Proportion of smokers among persons over 20 yr of age in sample population and among patients*[a]

City	Sample size	Population, %			Patients, %	
		Males	Females	Total	Males	Females
Shenyang	21,245	62.7	19.0	41.0	83.8	63.7
Anshan	41,441	57.0	15.9	36.9	86.6	62.9
Luda	20,009	65.9	8.0	38.3	83.2	52.6
Jinzhou	21,510	53.2	15.0	34.6	81.8	62.2
Fushun	63,419	65.9	17.7	42.2	93.4	66.4
Yinkou	6,165	60.7	14.6	38.2	84.8	75.6
Dandong	19,584	63.1	9.3	37.3	88.5	44.4
Liaoyang	20,783	65.5	16.7	41.5	81.1	91.7
Fuxin	14,383	68.8	20.1	45.9	93.8	62.3
Total	228,539	62.6	15.4	39.6	85.5	62.4
		(63.2)	(15.1)		(79.9)	(35.2)

[a] *Values in parentheses* are age-adjusted to the 1964 census.

reference standard (1 ng/m^3). The level of BP in Anshan (city 2), which has the largest steel factory in China, resembled that of Birmingham, Alabama (a steel-producing city in the U.S.) in 1958–59 (*4*). The mean levels of TSP were not correlated with the lung cancer mortality rates for these cities, and statistically nonsignificant positive correlations were observed for SO$_2$ and BP.

However, when we studied the correlation between the levels of pollution at the selected sites in Shenyang and the lung cancer mortality rates for the corresponding communes, they were significantly correlated. Table 6 shows the relationship between 1972 and 1973 TSP levels from 7 sites in Shenyang and the 1976–78 age-adjusted mortality rates for the local communes, with $r = .79$, $P < .05$. The relationship between the levels of falling dust at 12 sites in Shenyang, measured in 1955–57 (about 20 yr before the patients died) and the 1976–78 age-adjusted mortality rates for the local communes are presented in table 7; $r = .81$, $P < .01$.

The mortality rates of the population residing on Shenyang's Guongming Street, located within 2 km and downwind of a large nonferrous smelter, were significantly higher than the mortality rates in Shenyang during 1976–82 (table 8). Four communes located close to the main stacks of the Anshan Steel Company had the highest mortality rates in Anshan, but the rates were not significantly different from those for the other communities in Anshan.

DISCUSSION

The increased rate of lung cancer in urban compared with rural areas in many parts of the world has primarily

TABLE 4.—*Estimate of mortality rates of nonsmokers (1/100,000) by sex*

Sex	City	Person-yr observed	Estimated No. of nonsmokers	No. of nonsmokers among patients	Estimated mortality rates
Female	Shenyang	3,092,282	2,674,824	169	6.32
	Anshan	1,028,188	912,003	49	5.37
	Luda	1,502,724	1,409,555	83	5.89
	Jinzhou	431,625	385,872	17	4.41
	Fushun	1,289,875	1,133,800	33	2.91
	Yinkou	358,636	322,055	9	2.79
	Dandong	421,000	392,793	20	5.09
	Liaoyang	307,886	274,634	1	0.36
	Chaoyang	163,876	146,832	3	2.04
	Fuxin	567,273	496,931	7	1.41
Male	Shenyang	3,167,564	1,697,814	122	7.19
	Anshan	1,092,804	637,105	25	3.92
	Luda	1,585,453	726,137	60	8.26
	Jinzhou	453,464	273,892	18	6.57
	Fushun	1,363,408	721,242	16	2.22
	Yinkou	387,063	214,433	7	3.26
	Dandong	427,870	225,060	7	3.11
	Liaoyang	328,683	180,118	7	3.89
	Chaoyang	181,907	98,412[a]	2	2.03
	Fuxin	608,622	321,352	3	0.93

[a] Calculation is based on the average percentage of nonsmokers in the 9 cities.

TABLE 5.—*Average concentrations of TSP, SO_2, and BP in air of the 10 cities during 1980–82*[a]

City	TSP, mg/m^3			SO_2, mg/m^3		BP, ng/m^3		
	January	January and July	Highest value	January and July	Highest value	January	January and July	Highest value
Shenyang	0.58	0.43	1.13	0.19	1.16	49.1	28.6	140.6
Anshan	0.68	0.51	2.22	0.13	0.73	88.3	44.3	210.0
Luda	0.62	0.47	1.50	0.07	0.71	77.2	41.9	589.6
Jinzhou	0.91	0.62	2.45	0.24	1.01	172.0	88.9	289.3
Fushun	0.73	0.60	1.75	0.22	0.66	164.7	97.9	360.0
Yinkou	0.42	0.41	1.45	0.08	0.26	34.3	19.2	72.3
Dandong	0.36	0.34	0.83	0.11	0.45	43.8	37.5	140.3
Liaoyang	0.56	0.58	2.13	0.18	0.81	—	—	—
Chaoyang	0.84	0.65	2.83	0.08	0.30	71.0	49.6	249.0
Fuxin	0.52	0.40	2.43	0.12	0.64	33.9	24.8	157.4

[a] Highest value is based on daily average. *Dashes* indicate no data are available.

been attributed to smoking habits and occupational exposures. Air pollution has been thought to have little effect, if any, on lung cancer death rates. However, certain patterns of lung cancer mortality in large industrial cities in Liaoning cannot be explained by smoking and occupation alone.

Despite large differences in lung cancer mortality, we noted little difference in smoking prevalence in either sex among the 10 cities. Furthermore, we estimate that mortality rates for female nonsmokers are significantly higher in large industrial cities where lung cancer mortality rates for the total populations are higher. Despite the fact that smoking is three to four times more common in males than in females, the ratio of lung cancer mortality rates for males to those for females is only moderately elevated; it is 1.4- and 1.7-fold higher in Anshan and Shenyang, respectively. Furthermore, the mortality rates for females in these 2 cities were about twice those for U.S. white females, whereas those for males were much lower than rates for U.S. white males. These findings suggest some special risk factors for females in these large cities other than cigarette smoking. Circumstantial evidence from the Cancer Hospital of Liaoning Province supports this view. Of the patients whose lung cancers were diagnosed as adenocarcinomas, a histology generally seen less frequently in smokers, 26.4% were males and 58.8% were females (table 9).

Differences in the quantity and quality of occupational exposure and the years of exposure may account for part of the variation in mortality between large and small cities, particularly for males. We plan to examine this male difference in a case-control study. Interviews with relatives of the lung cancer patients revealed that 69% of the female patients were housewives, and only 11.4% were reported to have been exposed to the occupational carcinogens listed on the questionnaire. One interesting finding is that in 1 of the cities, Luda, 22 lung cancer patients (4.1%) were reported to have worked as cooks. This percentage seems excessive if one considers the small number of professional cooks compared with other professions in the city. (As noted earlier, only smoking data were collected from the population sample, so that estimates of risk associated with occupation cannot be calculated.) This may be a clue to the high frequency of lung cancer in housewives because their major task in the home is cooking.

A significant correlation was found between lung cancer mortality rates and air pollution within communes in Shenyang, not only with the recently monitored pollution data but also with those from the past.

TABLE 6.—*Relationship between lung cancer mortality rates and concentrations of TSP at various sites in local communes in Shenyang, 1972–73*[a]

Sample site	TSP, mg/m^3	Mortality rates/100,000[b]
1	1.08	30.66
2	0.89	24.96
3	0.54	20.28
4	0.58	17.11
5	0.61	16.80
6	0.38	17.61
7	0.77	15.87

[a] $P<.05$; $r = .79$

[b] Mortality rates were age-adjusted to 1976–78.

TABLE 7.—*Relationship between lung cancer mortality rates and concentrations of falling dust (measured in 1955–57) in local communes in Shenyang*[a]

Sample site	Falling dust, tons/km^2	Mortality rates/100,000[b]
1	1,328.3	24.96
2	1,207.9	37.78
3	967.8	29.56
4	804.8	23.11
5	780.1	20.87
6	743.8	15.74
7	660.4	24.48
8	608.7	19.70
9	428.7	19.15
10	421.7	16.14
11	361.5	9.83
12	358.7	11.70

[a] $P<.01$; $r = .81$

[b] Mortality rates were age-adjusted to 1976–78.

TABLE 8.—*Age-adjusted mortality rates and observed and expected cases during 1976-82*[a]

Yr	Mortality rates		No. of cases		Relative risk	χ^2	*P*
	Guongming	Shenyang	Observed	Expected			
1976–78	24.96	17.65	13	9.96			
1979–82	30.27	22.76	26	16.64			
			39	26.60	1.47	5.78	<.05

[a] Mortality rates of Shenyang were used as a standard. Persons studied resided on Guongming Street in Shenyang.

TABLE 9.—*Percentages of patients with histologic types of lung cancer admitted to Cancer Hospital of Liaoning Province*

Types of lung cancer	Males		Females	
	No.	Percent	No.	Percent
Squamous cell	34	39.1	7	20.6
Adenocarcinoma	24	26.4	20	58.8
Nondifferentiated	26	29.9	7	20.6
Others	4	4.6	0	0.0
Unknown	18		6	

Levels of air pollution (TSP) are not correlated with the mortality rates of the 10 cities studied. It is not clear why the correlation would be significant only within Shenyang but not among the 10 cities. However, we found it difficult to evaluate pollution because 1) current levels of pollution do not necessarily represent the past situation, especially in some newly developing cities, 2) urban air pollution changes from place to place and from time to time, so samples collected from a few sites may not be representative of the city as a whole or of the relevant period preceding cancer onset, and 3) TSP, SO_2, and BP may not be the most appropriate indices for evaluating the carcinogenic risk of air pollution. Investigators (*5-7*) conducting several studies have suggested that residents living near smelters, steel foundries, and petrochemical factories, which emit not only BP but also many metallic particles and chemical agents known or suspected to be carcinogens or co-carcinogens, are more likely to die from lung cancer.

Crowded residential conditions may also be involved in the higher rates in Shenyang and Anshan and other urban areas of China. The large number of stoves in a small area concentrates neighborhood and indoor air pollution and shortens the distance of individuals from domestic sources of pollution, primarily coal stoves for cooking and heating. Pollution becomes worse in winter, when the ventilation in rooms is poor. In northern China, when winter comes, people seal the windows and heat their rooms with bituminous coal stoves with an exhaust pipe made of tinplate and consisting of connected parts, so that the indoor air is often filled with smoke and soot. We consider the north–south gradient in lung cancer mortality among cities within China noteworthy. Tables 10 and 11 show significant correlations between high latitude and lung cancer mortality rates for females in the 16 most populous cities (>1,000,000 according to the 1953 census) and 10 other

TABLE 10.—*Relationship between latitude and age-adjusted mortality rates of cities with >1,000,000 population by different cancers and sex*[a]

Metropolitan area	Latitude, degrees	Lung cancer		Bladder cancer	
		Male	Female	Male	Female
Harbin	45.8	19.28	11.67	.77	.62
Changchun	44.1	18.30	12.49	1.07	.53
Shenyang	41.9	18.55	12.31	1.08	.61
Fushun	41.9	17.17	8.60	1.07	.48
Beijing	39.9	14.84	11.31	1.20	.69
Tianjing	39.1	14.03	11.49	1.88	.70
Luda	38.8	24.27	12.08	1.18	.20
Tianyuan	37.9	17.04	7.12	—	—
Qingdao	36.1	14.48	9.05	—	—
Xian	34.3	11.25	6.40	1.38	.44
Nanjing	32.0	15.58	6.17	1.22	.43
Shanghai	31.2	29.31	10.81	2.62	.87
Chengdu	30.8	10.57	5.20	1.44	.84
Wuhan	30.7	13.19	4.73	—	—
Chongqing	29.6	17.55	8.27	.74	.32
Guangzhou	28.1	15.14	8.02	—	—
r		.17	.69[b]	−.38	−.048
β		.14	.33	−.03	−.002

[a] Population is according to 1953 census. *Dashes* indicate no data are available. β = regression coefficient.

[b] $P < .01$.

TABLE 11.—*Relationship between latitude and age-adjusted mortality rates of cities with >500,000 population by different cancers and sex*[a]

City	Latitude, degrees	Lung cancer		Bladder cancer	
		Male	Female	Male	Female
Jilin	44.2	18.10	11.97	1.02	.51
Shijiazhong	38.0	16.17	10.04	.94	.40
Jinan	36.8	19.02	10.12	—	—
Zhengzhou	34.8	13.97	5.12	1.48	.31
Hangzhou	30.3	22.63	7.58	1.77	.84
Nanchang	28.8	12.48	6.85	.40	.32
Changsha	28.2	23.98	10.50	1.37	.78
Guiyang	26.7	9.88	3.83	.98	.42
Fuzhou	26.1	10.16	4.74	1.23	.32
Kunming	25.0	9.63	2.88	1.28	.69
r		.39	.75[b]	−.09	−.174
β		.33	.38	−.006	−.006

[a] *See* footnote *a*, table 10.

[b] $P < .02$.

large cities ($>500{,}000$) as well, with $r = .69$, $P<.01$, and $r=.75$, $P<.02$, respectively. The correlations are positive but of a lower order of magnitude and not statistically significant for males. This strong correlation did not exist for other smoking-related cancers (note the low correlation coefficients for bladder cancer). Although many factors may be associated with latitude, such as cold weather increasing the incidence of chronic respiratory tract disease and decreasing vegetable production, these influences should be approximately the same on males as on females. Thus levels of indoor air pollution may influence the geographic variation in lung cancer mortality.

In summary, although no definitive inferences can be made from this type of correlation study, the results raise the hypothesis that neighborhood air pollution and indoor air pollution from cooking and fumes from burning coal, aggravated by crowded living conditions, may contribute to the relatively high risk of lung cancer in females in large industrial cities. A case–control study is warranted in high-risk districts of large industrial cities, with all potential risk factors taken into consideration and with special attention to those affecting nonsmoking housewives.

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Opportunities for United States–People's Republic of China Collaboration in Cancer Epidemiology [1]

Joseph F. Fraumeni, Jr. [2]

The presentations at this session have highlighted the exceptional opportunities for cancer epidemiology that exist in China. To a large extent, the opportunities can be traced to the remarkable cancer atlas from China, which revealed a surprising degree of geographic variation and a series of important etiologic clues. Several of the clues are now being pursued by case–control studies of selected cancers in high-risk areas, and, in many projects, Chinese epidemiologists are collaborating closely with investigators from the U.S. During this session, we have heard in some detail about the cooperative program of studies supported by a contract between the U.S. National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences. These involve case–control studies of esophageal cancer in Linxian, stomach cancer in Shandung, lung cancer in Shanghai, and choriocarcinoma in Beijing. Also in the pilot stages is an intervention study in Linxian involving vitamin and mineral supplements in which epidemiologists hope to determine whether nutritional improvements inhibit the development of esophageal cancer in the general population and among those at exceptional risk by virtue of their having esophageal dysplasia. All the projects under way deal with important scientific and public health problems and deserve the highest priority so that successful completion is ensured, including the application of all promising experimental techniques and the vigorous pursuit of new leads by appropriate investigations.

Mention should be given to other projects which are under way or being considered under the aegis of the U.S.–China program. In its early stages is a survey of leukemia and lymphoma being conducted by the Chinese to determine whether the elevated mortality rates in the eastern and northeastern provinces represent an extension of the focus of T-cell leukemia across the sea in the southwestern part of Japan. They will also examine the cell types of these neoplasms and the possible role of the human T-cell leukemia virus. Preliminary data from China were presented by Zhang and co-workers to suggest geographic variation of T-cell lymphomas, with a high frequency in certain eastern regions, particularly around the lower reaches of the Yangtze River.

Collaborative case–control studies of other cancers are also taking place in high-risk areas of China. Evidence indicates that hepatocellular carcinoma along the southeastern coast is related to hepatitis B virus infection, and field vaccination trials are being planned. It is interesting that hepatitis B has been related to liver cancer among Chinese Americans and has led to vaccination trials in this group also. However, in China and elsewhere, further studies are needed if investigators are to clarify interactions with other possible risk factors, including alcohol, smoking, and aflatoxin. In some parts of China, about 5% of liver cancer consists of cholangiocarcinoma (intrahepatic bile duct cancer), which appears related to biliary tract infection by the liver fluke, *Clonorchis sinensis.*

Another important discovery from the Chinese Atlas was the overlapping of endemic areas for colorectal cancer with those for *Schistosomiasis japonica.* Case–control studies of colorectal cancer among Chinese in China and the U.S. are under way, supported by a grant from the NCI to Stanford University. Dr. Whittemore and colleagues hope to gain insight into the relationships of bowel cancer to schistosomal infections and other suspected risk factors.

Extremely high rates of nasopharyngeal cancer occur in southern China, where further collaborative studies should clarify the role of salted fish and other dietary items, occupational exposures, the Epstein-Barr virus, and genetic markers including histocompatibility antigens. Some remarkable familial aggregations were reported in this session by Li and associates and deserve special study in a search for genetic and environmental determinants.

The rates for cervical cancer are high in parts of Central China and overlap with the rates for penile cancer, which suggests a common factor in the etiology of both tumors. Consideration should be given to initiation of studies of cervical cancer and possibly penile cancer in high-risk areas for an understanding of the possible venereal transmission of herpes virus type 2 and human papillomavirus, and the role of nutritional deficiency, smoking, and other exposures.

The importance of cell type distinctions in cancer epidemiology is illustrated by several observations, notably the high rates of lung adenocarcinoma reported among Chinese women. Another example from the recent literature is the low frequency of Ewing's sarcoma reported among patients with bone cancer, a pattern resembling that seen in Japan and in the U.S. black population. Also, a pathology survey of brain tumors in China has revealed

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ABBREVIATIONS: NCI=National Cancer Institute; NPC=nasopharyngeal carcinoma.

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[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

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high frequencies of craniopharyngiomas and teratoid tumors (pinealomas) as compared with Western countries, a pattern also described by the Japanese. Studies of cancer in young people should be worthwhile, particularly in view of the high rates reported for myeloid leukemia and liver cancer (hepatoblastoma?) among children in Shanghai. Whenever possible, studies of selected cancers should be designed to delineate the role of precursor lesions, such as esophageal dysplasia, chronic atrophic gastritis, schistosomal polyps, and hydatidiform mole.

In addition to the geographic variation of cancer in China, time trends are of special interest. In Shanghai, rapid increases have been reported in the rates for cancers of the lung, large bowel, pancreas, and bladder, in addition to significant decreases in cervical cancer. Also apparent are some recent increases for cancers of the breast, endometrium, and ovary that are perhaps related to delays in marriage and childbearing or to changing dietary habits. Case–control studies of tumors on the rise in China should be encouraged in appropriate areas, such as the study of breast cancer recently initiated in Tianjin, a comparatively high-risk area on the cancer maps.

With the development of U.S.–China collaborative research, investigators are trying to identify potentially carcinogenic exposures that deserve epidemiologic study. For example, the influence of low levels of ionizing radiation may be clarified by a joint U.S.–China survey of thyroid neoplasms being considered for Yangjiang, where in some areas the level of background radiation is three times that of neighboring areas.

Occupational problems also appear abundant, particularly because of the rapid industrialization of China since the 1950s. Of special interest are the tin miners in Yunnan who are exposed to high levels of radon and inorganic arsenic and who also provide opportunities for evaluation of the interactions with smoking. Because coal is the major energy source in China, pneumoconiosis and silicosis are common ailments, and it may be possible to determine whether silica is carcinogenic as suggested by some investigators. The large cotton textile industry provides opportunities for researchers to clarify possible relationships with nasal, bladder, and other cancers as previously suggested. Inasmuch as pesticides are in widespread use in rural areas, there is obvious potential for evaluation of the carcinogenic risks of these compounds.

The chemical industry has flourished in recent years, so the effects of many agents in current use may be investigated, including asbestos, benzene, vinyl chloride, benzidine, chromates, haloethers, arsenic, and coal tar derivatives. These exposures were identified in a national survey of occupational cancer hazards conducted in 1982 by the Ministry of Health in China.

Because the Chinese population depends on coal as an energy source, special emphasis should be placed on studies that will help evaluate the effects of air pollution from coal combustion products, notably polycyclic hydrocarbons. This may occur through outdoor or indoor pollution. An interesting area for study is Xuanwei, where the rates for lung cancer are high for both sexes, possibly due to outdoor exposures in the midst of this coal industry region or indoor exposures in poorly ventilated homes heated by coal. Other pollutants may prevail in different regions of the country. Thus in Shenyang, assessment of the carcinogenic potential of arsenical emissions released into the community from nonferrous smelters should be possible.

The escape of chemicals into the drinking water may also affect the risk of certain cancers; e.g., high levels of halogenated hydrocarbons are reported in some areas where liver cancer is common, and inorganic arsenic is common around the Yunnan tin mines where skin cancers appear to arise in conjunction with arsenical dermatoses.

Unique opportunities may develop also from the widespread use of herbal medicines in China. Some are known to contain arsenic, whereas others combine phenylbutazone with aminopyrine, agents with potential bone marrow toxicity. It is interesting that these herbal medicines are also available over the counter in some parts of the U.S.

Recent attention in cancer epidemiology in China has focused on dietary and nutritional hypotheses, particularly through case–control studies in high-risk areas. To date only a few geographic areas have been selected for investigation, and examination of the cancer maps indicates many more potential study populations. For example, several widely separated areas are endemic for stomach and esophageal cancer. It will be interesting for epidemiologists to determine whether the same risk factors uncovered by the current studies prevail in other high-risk locations, or if separate risk factors are operating. In addition, a cluster of NPC appears in Sichuan, although anecdotal reports suggest historical migration from high-risk areas of South China. Besides case–control studies, insights into nutritional factors are also being sought by those conducting correlational and cohort studies. An NCI grant to Cornell University is supporting collaborative surveys of cancer risk among Chinese populations exposed to varying levels of selenium as measured in soil and blood samples. This study is important in view of some experimental and epidemiologic observations linking low selenium intake with certain cancers. A selenium deficiency syndrome manifested by diffuse cardiomyopathy has been described in China, and investigators plan to evaluate the cancer experience of this group in follow-up studies.

In his introductory remarks at this meeting, Dr. Zhang emphasized the importance of biochemical and molecular epidemiology, i.e., the integration of laboratory techniques with epidemiologic approaches. Especially promising are methods described for measurement of endogenous formation of nitrosamines, aflatoxin metabolites, carcinogen–DNA adducts, and susceptibility mechanisms such as DNA repair defects. Although the cancer maps of China reflect the importance of life-style and other environmental forces in the origins of cancer, the role of host factors should not be neglected in further epidemiologic and multidisciplinary research.

Although no one mentioned them during this session, studies of animal models in China have received some attention in the literature and may help clarify the role of dietary and other carcinogens. These include the observations of gullet cancer in chickens in areas where human esophageal cancer is endemic, nasal tumors in pigs where NPC is commonplace, and liver cancer in ducks infected by hepatitis B where human liver cancer is also prevalent.

Another opportunity for epidemiologic study is provided by the experience of Chinese migrant populations, such as those moving to Singapore or the U.S. Continuation of descriptive and analytical studies conducted in parallel among Chinese, both on the mainland and in other countries, should be encouraged. The operation of the Shanghai Tumor Registry since the early 1960s has been essential for the measurement of cancer incidence and mortality, and the development of population-based registries in other parts of China will be important in view of the major geographic and ethnic variations of cancer throughout the country.

Because of the changing risks and heterogeneous exposures of migrant groups, chances for risk factor identification are enhanced through analytical epidemiology, particularly studies incorporating biochemical measurements such as MacMahon and Henderson and their colleagues conducted with respect to hormones and breast cancer. This tumor has shown a slow upward displacement of risks among Chinese and Japanese populations migrating to the U.S. A detailed evaluation of nutritional and hormonal status among Oriental females developing breast cancer under age 55 is now under way in California and Hawaii in collaboration with the NCI. Similar studies might be conducted in urban areas of China where rates of breast cancer are increasing.

Colon cancer is also amenable to the strategy of migrant studies, so that ongoing investigations in both China and the U.S. should help elucidate reasons for the increasing risks that have developed quickly among Chinese migrants to this country. In contrast, the rates for NPC have declined in Chinese migrants but still appear elevated over the base-line risk among U.S. whites, which suggests the value of our searching for genetic markers as well as environmental and dietary exposures that persist among the migrants. The elevated risks of lung cancer, especially adenocarcinoma, among Chinese women in various parts of the world still await explanation. Also interesting is the fact that the rates for thyroid cancer are higher in Chinese Americans than in other ethnic groups, particularly in Hawaii, so that comparative surveys in China will be valuable. Because Chinese populations are not concentrated in sufficient numbers in any single area of the U.S., analytical studies will obviously require the collaboration of different groups, especially in Hawaii, San Francisco, and Los Angeles. It is fortunate that these areas are well covered by population-based cancer registries.

The low rates of prostate cancer in China received little attention, and the apparently slow increase in risk among Chinese migrants in the U.S. also deserves further study, along the lines of research used with Japanese migrants. The low rates for certain lymphoproliferative neoplasms, including chronic lymphocytic leukemia and Hodgkin's disease, also should be investigated in China and among migrant groups, so that host and environmental factors can be distinguished.

In summary, enormous potential exists in China for epidemiologic research in cancer. Opportunities are enhanced by the large and accessible populations and by the supportive and cooperative nature of the social organization, health services, and research institutes. The striking geographic and demographic patterns uncovered by the cancer atlas have generated fresh etiologic hypotheses, and the migration of populations within and outside China provide further strategies for epidemiologic research. Although the accomplishments of Chinese epidemiologists have been great over a short time, their resources are limited, and progress is likely to be accelerated by continued close communication and collaboration with scientists in the U.S. The recent exchanges of epidemiologists for purposes of training and research have been most successful, as has been our experience to date with all the collaborative projects. Investigators from China and the U.S. have displayed a cooperative spirit and dedication that have overcome the long distances that separate our two countries. These efforts have helped establish a solid foundation for future collaborative projects designed to increase our understanding of the causes of cancer and the means to prevent it.

SESSION II

Cancer Incidence Among Ethnic Populations in Different Areas of the Pacific Basin

Cancer Incidence in Caucasians Living in the Pacific Basin [1, 2]

Anne McTiernan, Joseph Chu, *and* David B. Thomas [3]

ABSTRACT—Variations in cancer incidence among whites in 1973-77 in 8 geographic areas of the Pacific Basin were compared. Substantial differences were found for the occurrences of lung cancer, cancer of the corpus uteri, and malignant melanoma. White women living in New Zealand and Australia had the lowest risk of developing lung cancer, whereas white men living in the western United States had the highest risk. Cancer of the corpus uteri occurred more commonly in the western United States than elsewhere in the Pacific Basin. Geographic areas located closest to the equator experienced the highest incidence of malignant melanoma. In all areas, the incidence rates of cancers of the lung and corpus uteri and malignant melanoma increased significantly between 1960-66 and 1973-77; after the mid-1970s, rates of cancer of the corpus uteri declined. The incidence of stomach cancer decreased in all areas. Although cervical cancer decreased in incidence over time for most women, it increased noticeably in young women. The incidence of breast cancer also rose during the 17-year period. In at least 1 geographic area, the observed increases in breast cancer incidence were confined to women under age 40. — Natl Cancer Inst Monogr 69: 65-72, 1985.

The white populations residing in the various geographic areas of the Pacific Basin may differ greatly in their exposures to cancer-causing factors. The different cultural and physical environments that these groups experience may be as varied as those of different races within a single geographic area. Temporal and geographic variations in incidence rates of cancer in whites may therefore provide clues to the identification of unknown causes of cancers. In this paper, these variations are presented for the more common neoplasms that occur in whites of the Pacific Basin.

MATERIALS AND METHODS

Incidence rates were obtained for 9 geographic areas of the Pacific Basin covered by population-based cancer registries [(*1*); Henderson BE: Personal communication]. These registries are located in British Columbia, Canada; Seattle, Washington, Alameda County and Los Angeles, California, and Hawaii, U.S.; New Zealand; New South Wales, Australia; South Australia; and New Caledonia. The incidence rates for New Caledonia were low for virtually all cancers. As this may have been due to incompleteness of reporting, rates for this area, although presented, have not been considered in the comparative discussions. Rates for all areas except British Columbia and New South Wales are specific for whites. The rates for these latter 2 areas include all races combined, but because the majority of persons in these areas are white, the rates are assumed to represent rates for whites.

Incidence rates for different periods have been published (*1–3*) for British Columbia, Alameda County, New Zealand, and Hawaii; examinations of trends over time are limited to these 4 geographic areas. All incidence rates presented have been age-adjusted to the 1970 world population.

Information is presented only for cancers with incidence rates equal to or greater than 5 cases per 100,000 persons per year for men and women in most geographic areas. Comparisons of incidence rates of rarer cancers were not made because variations among geographic areas could be due to random fluctuation or differences in completeness of reporting. The sites included for comparison were: stomach, colon, rectum, pancreas, lung, bladder, melanoma, prostate, female breast, corpus uteri, ovary, and cervix uteri.

COMPARISONS AMONG GEOGRAPHIC AREAS

Table 1 presents average annual incidence rates of 6 selected cancers among white men and women for the years 1973–77.

Although the incidence of lung cancer in men remained uniform at 50 to 60/100,000, the incidence of this cancer in women ranged from 8.6 to 24.1 per 100,000 per year. Women residing in the western areas of the United States and in Hawaii had a two to three times greater risk of developing lung cancer than women living in British Columbia, New Zealand, and Australia.

Men and women residing in New Zealand and New South Wales were about one-half as likely to develop bladder cancer as were those living in other areas of the Pacific Basin. Although white Hawaiian men were at high risk of getting this cancer, white Hawaiian women were at low risk.

For both sexes, the incidence rates of stomach cancer were lowest in Seattle and highest in New Zealand, and the ratio of the New Zealand to the Seattle rates was 1.8.

The occurrence of pancreatic cancer was notably similar in all geographic areas, with about 8 or 9 new cases occurring per 100,000 men and 5 or 6 cases per 100,000 women per year.

The variation in the occurrence of colon cancer was less than that in stomach cancer and was not consistent between the 2 sexes. Los Angeles had the highest incidence of this cancer in men, whereas New Zealand had the greatest incidence in women.

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[2] Supported in part by Public Health Service grant CA34958 from the National Cancer Institute.

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TABLE 1.—*Annual age-adjusted incidence rates per 100,000 of selected cancers in white residents of the Pacific Basin (1973–77)*

Area	Lung		Bladder		Stomach		Pancreas		Colon		Rectum	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
British Columbia, Canada	49.0	14.1	19.2	5.6	13.6	6.3	8.2	5.6	21.5	21.1	14.9	10.3
Seattle, Washington	63.4	22.2	21.3	5.8	9.1	4.0	8.5	5.6	25.9	23.0	15.2	9.5
Alameda County, California	64.4	24.1	19.6	6.1	10.5	4.5	9.2	6.0	25.6	22.9	14.6	9.1
Los Angeles, California	58.6	22.4	23.6	6.2	9.5	4.6	8.1	5.0	28.0	24.3	14.7	10.00
Hawaii	64.2	23.1	23.5	3.9	12.2	5.0	8.6	6.5	25.3	17.8	14.1	8.9
New Zealand	53.2	11.5	12.8	3.4	16.3	7.0	8.6	5.0	25.5	26.9	16.1	11.2
New South Wales, Australia	51.4	8.7	14.7	4.1	13.7	6.7	8.1	4.7	21.5	18.0	12.8	8.4
South Australia	54.5	8.6	21.7	4.6	13.8	6.1	9.2	5.9	22.9	21.6	13.0	8.6
New Caledonia	48.0	7.0	7.3	1.0	11.1	4.7	3.1	2.4	12.2	9.4	11.8	5.6

In all areas considered, incidence rates were lower for rectal than colon cancer, but the geographic variation in rates of neoplasms at these 2 sites were similar.

The incidence of melanoma in whites varied greatly among the 8 geographic areas. As shown in figure 1, the incidence of melanoma decreased with increasing latitude of the registry area. The only notable exception to this trend was Hawaii: It has the lowest latitude and yet had intermediate rates of melanoma. A least-squares regression analysis indicated that each 1° decrease in latitude was associated with 0.27 and 0.15 new cases of melanoma per 100,000 men and women, respectively, per year.

One type of melanoma, Hutchinson's Melanotic Freckle, may have different etiologies than other types of melanoma (*4*). We compared incidence rates of melanomas of the head and neck (25% of which are the melanotic freckles) with the incidence of other types of melanomas combined (1–2% of which are Hutchinson's melanotic freckles). There appeared to be little difference in the effect of latitude on the occurrence of these 2 classifications of melanomas.

Table 2 presents incidence rates for sex-related cancers. With an incidence of prostate cancer of about 59/100,000 per year, whites living in Seattle and Hawaii had a twofold increase in risk of developing this cancer, compared with those living in New Zealand and New South Wales.

In women, breast cancer incidence ranged from a low of 53.2 per 100,000 per year in New South Wales to a high of 85.6 per 100,000 per year in Hawaii. A direct, positive relationship between the incidences of prostate cancer and female breast cancer is shown in figure 2.

White women living in the western United States had a three times greater risk of developing cancer of the corpus uteri than those living in other areas of the Pacific Basin. The highest annual incidence rate per 100,000 women (38.5) was observed for Alameda County, and the lowest rate (7.9) was observed for New South Wales.

The incidence of ovarian cancer was higher in the western United States and British Columbia than in New South Wales, New Zealand, and South Australia.

Invasive cervical cancer occurred at similar rates around the Pacific Basin, ranging from 9.2 in South Australia to 12.5 cases per 100,000 women per year in New South Wales.

TRENDS IN CANCER INCIDENCE OVER TIME

Increases in the incidence of lung cancer have occurred in most areas of the Pacific Basin (tables 3, 4). These increases occurred in both men and women, but the proportional rate of increase in women was appreciably larger. Among white men living in Hawaii and Alameda County, the annual incidence of lung cancer rose from about 46/100,000 in 1960–66 to 64/100,000 in 1973–77. In 1960–66, the annual incidence of lung cancer in women ranged from 6 to 10/100,000. Two decades later, the incidence in women had doubled in Hawaii and New Zealand, and it had tripled in Alameda County. More recent data from the Seattle area (fig. 3) indicate that the incidence of lung cancer is continuing to rise in women but has stabilized in men.

The occurrence of stomach cancer decreased between 1960–66 and 1973–77 by about 20–40% in both men and

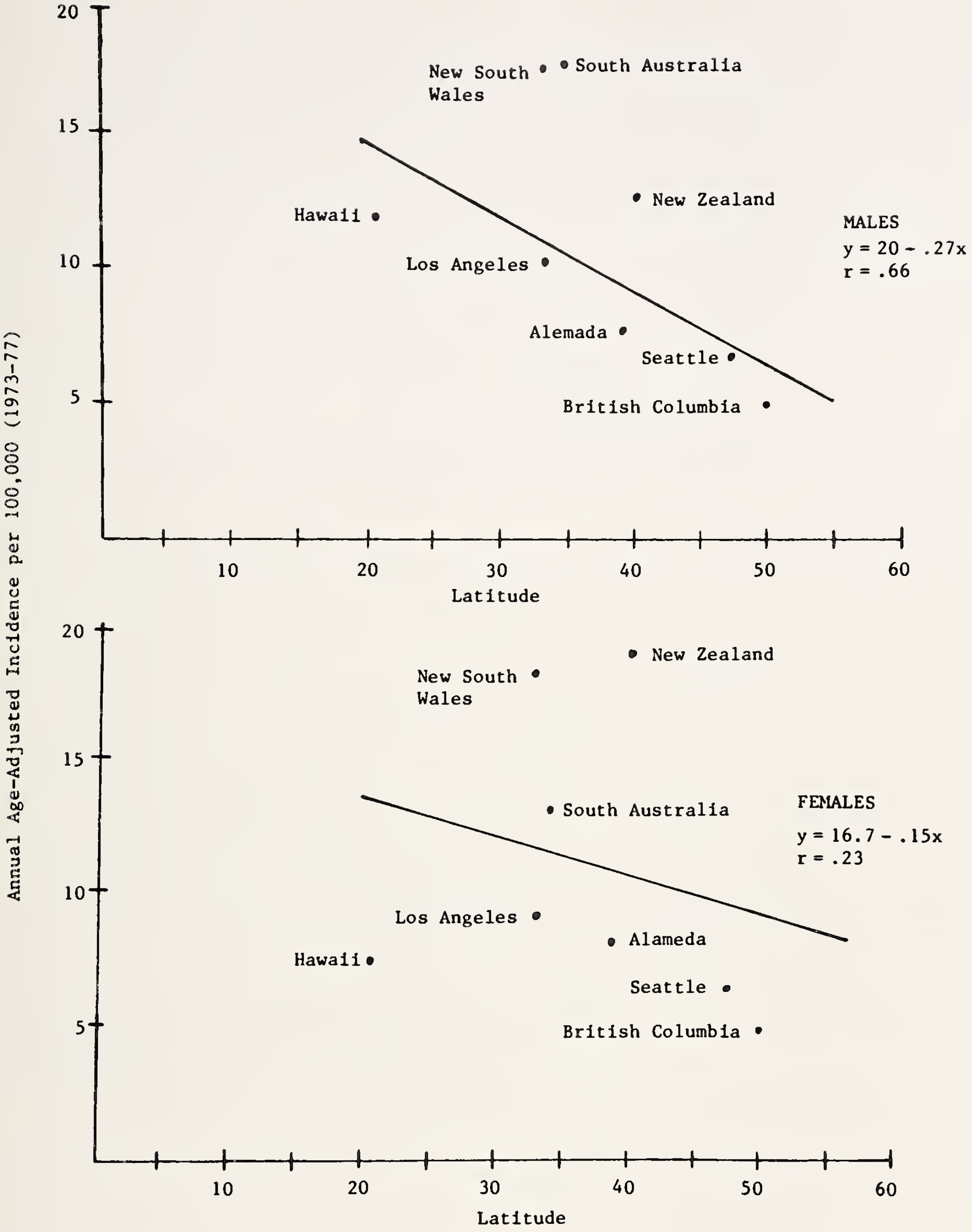

FIGURE 1.—Occurrence of malignant melanoma in the Pacific Basin by latitude (1973–77).

TABLE 2.—*Annual age-adjusted incidence rates per 100,000 of sex-related cancers in white residents of the Pacific Basin (1973–77)*

Area	Males	Females			
	Prostate	Breast	Corpus uteri	Ovary	Cervix uteri
British Columbia, Canada	39.8	72.8	20.5	12.2	12.2
Seattle, Washington	58.6	76.5	35.8	12.5	11.0
Alameda County, California	44.5	78.2	38.5	14.0	10.3
Los Angeles, California	44.3	85.3	35.2	13.9	10.2
Hawaii	59.7	85.6	34.8	9.4	9.3
New Zealand	30.7	62.6	11.2	11.3	10.8
New South Wales, Australia	28.4	53.2	7.9	9.0	12.5
South Australia	39.6	53.6	15.0	10.3	9.2
New Caledonia	23.6	37.6	12.7	7.4	18.4

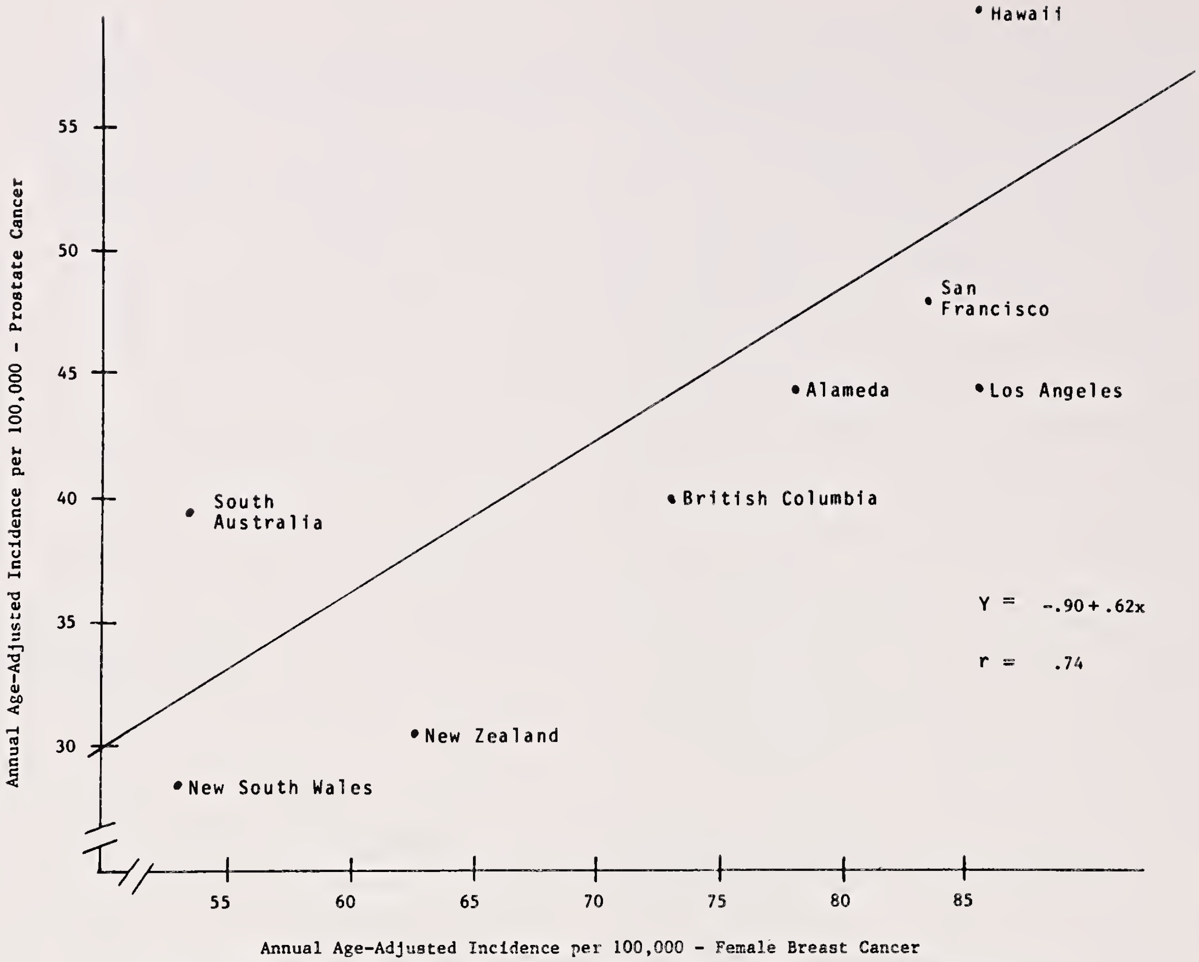

FIGURE 2.—Incidence of prostate and female breast cancers in the Pacific Basin (1973–77).

women with the greatest decreases occurring in Hawaii and Alameda County.

As well as being stable across geographic areas, the occurrence of pancreatic cancer was stable over time in all of the 4 geographic areas (British Columbia, Alameda County, Hawaii, and New Zealand). Cancers of the colon, rectum, and bladder also varied little in incidence over time.

In 3 of these 4 areas, the incidence of malignant melanoma doubled in two decades; the largest absolute increase was seen in New Zealand women. In addition, the rate of increase in men and women living in New Zealand was substantially larger between 1967–73 and 1973–77 than between 1960–66 and 1967–73.

The time trends for prostate cancer incidence show minimal change. Only Hawaii experienced a substantial increase since 1973–77.

An increase in the incidence of breast cancer was noted in

TABLE 3.—*Time trends in incidence of selected cancers in 4 areas of the Pacific Basin (males)*[a]

Site/type	British Columbia		Alameda County			Hawaii			New Zealand		
	1967–73	1973–77	1960–66	1967–73	1973–77	1960–66	1967–73	1973–77	1960–66	1967–73	1973–77
Lung	53.2	49.0	47.8	55.5	64.4	43.8	52.2	64.2	45.1	48.8	53.2
Bladder	20.6	19.2	17.9	19.2	19.6	19.3	18.7	23.5	12.1	10.8	12.8
Stomach	15.8	13.5	15.3	10.0	10.5	16.9	17.4	12.2	19.1	15.3	16.3
Pancreas	9.5	8.2	8.5	9.5	9.2	7.1	9.5	8.6	9.4	7.3	8.6
Colon	23.5	21.5	24.0	25.3	25.6	19.3	23.9	25.3	24.7	23.0	25.3
Rectum	15.9	14.9	15.5	15.0	14.6	12.6	13.5	14.1	15.6	15.4	16.1
Melanoma	3.6	5.0	3.8	5.4	7.5	4.5	6.8	11.8	6.2	7.4	12.3
Prostate	40.8	39.8	38.0	40.4	44.5	43.4	42.3	59.7	40.0	25.9	30.7

[a] Average annual incidence is per 100,000, age-adjusted to 1970 World Population.

TABLE 4.—*Time trends in incidence of selected cancers in 4 areas of the Pacific Basin (females)*[a]

Site/type	British Columbia		Alameda County			Hawaii			New Zealand		
	1967–73	1973–77	1960–66	1967–73	1973–77	1960–66	1967–73	1973–77	1960–66	1967–73	1973–77
Lung	11.2	14.1	7.4	18.9	24.1	10.2	18.9	23.1	6.1	8.0	11.5
Bladder	5.9	5.6	5.6	5.1	6.1	5.9	5.2	3.9	2.4	2.6	3.4
Stomach	6.0	6.3	7.4	5.3	4.5	8.8	6.6	5.0	9.5	6.2	7.0
Pancreas	5.5	5.6	5.6	6.3	6.0	5.0	7.4	6.5	5.1	3.8	5.0
Colon	18.5	21.1	22.9	22.2	22.9	27.5	22.9	17.8	25.0	23.2	26.9
Rectum	6.9	10.3	10.1	10.2	9.1	9.8	12.0	8.9	9.7	10.1	11.2
Melanoma	4.8	5.2	3.9	5.9	8.2	3.5	5.7	7.5	9.1	11.7	18.8
Breast	80.0	72.8	62.4	76.1	78.2	62.9	80.3	85.6	50.2	52.5	67.6
Corpus	17.4	20.5	16.8	33.3	38.5	17.5	28.8	34.8	10.6	10.4	11.2
Ovary	14.0	12.2	12.6	13.5	14.0	14.8	13.7	9.4	11.9	11.4	11.3
Cervix	[b]	[b]	17.9	12.3	10.3	15.4	13.1	9.3	13.9	9.9	10.9

[a] Average annual incidence is per 100,000, age-adjusted to 1970 World Population.

[b] Published data from British Columbia include in situ cases of cervical cancer and therefore are not comparable to data from other registries.

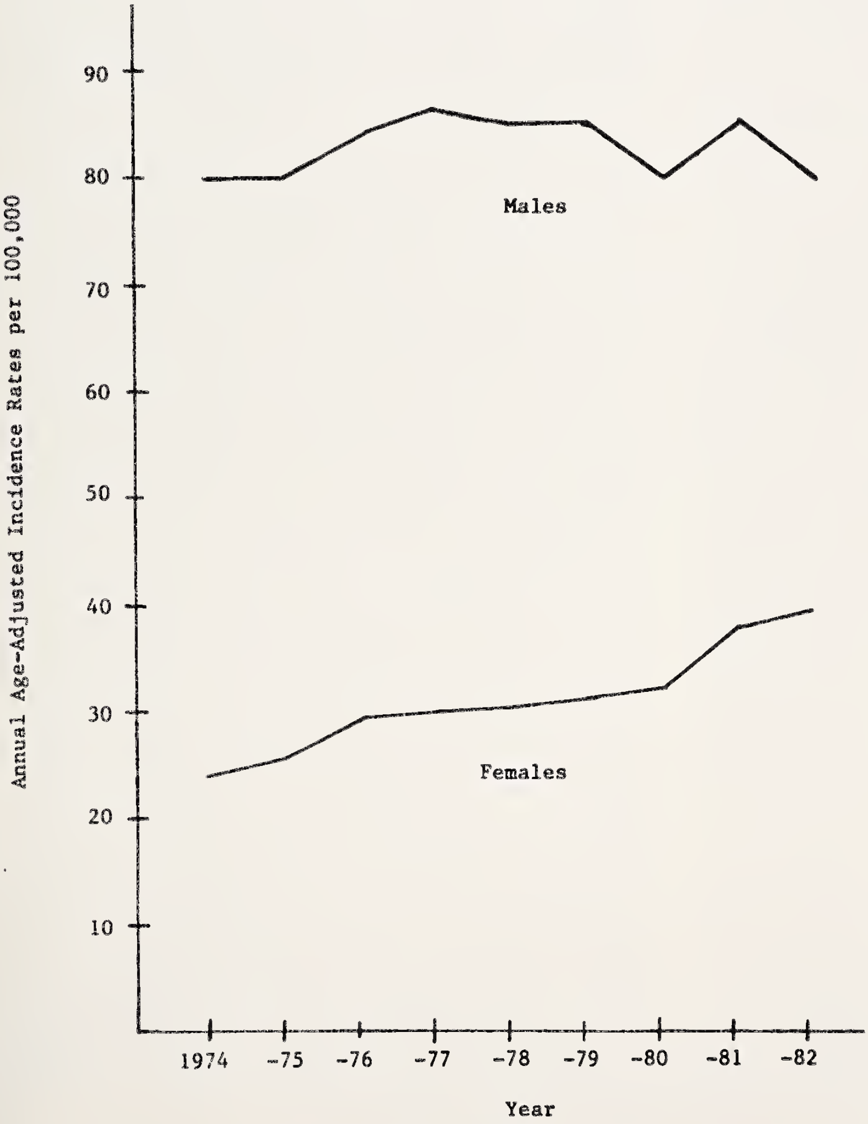

FIGURE 3.—Time trend of lung cancer in western Washington.

TABLE 5.—*Time trend of age-adjusted incidence of breast cancer in western Washington in women aged 20–44 yr and 45 yr and older*

Yr	Incidence at age:	
	20–44 yr	≥45 yr
1974	32.9	291.7
1975	28.2	267.6
1976	31.3	257.3
1977	33.5	228.4
1978	34.2	246.4
1979	36.5	255.5
1980	32.8	239.2
1981	38.1	249.6
1982	41.2	234.9

the 3 areas that provided data from 1960–66 to 1973–77. No increase was observed in British Columbia between 1967–73 and 1973–77. More recent time trends in western Washington are shown in table 5. Between 1974 and 1982, a 25% increase in breast cancer was seen in 20- to 44-year-old women. In older women, a slight decline in incidence was observed.

The incidence of cancer of the corpus uteri increased significantly in the United States until the mid 1970s, but more recent data suggest that this trend has reversed. Since 1975, the incidence of cancer of the corpus uteri has decreased steadily in the Seattle area (fig. 4).

Ovarian cancer did not vary substantially in incidence over time in any of the 4 areas examined.

The incidence of invasive cervical cancer declined steadily between 1960–66 and 1973–77 in Hawaii and Alameda County and to a lesser extent in New Zealand. (Data from British Columbia were not presented because in situ cases were included in the data published from the British Columbia registry.) The changes over time were found to differ markedly with age. The incidence of cervical cancer increased in recent years in women under age 40 but continued to decline in older women (table 6).

DISCUSSION

Some apparent differences in cancer incidence among geographic areas may have been due to differences in quality of data. Data from British Columbia and New South Wales included all races combined and may not be completely representative of the rates for whites. Slight variations in incidence rates may be a reflection of small

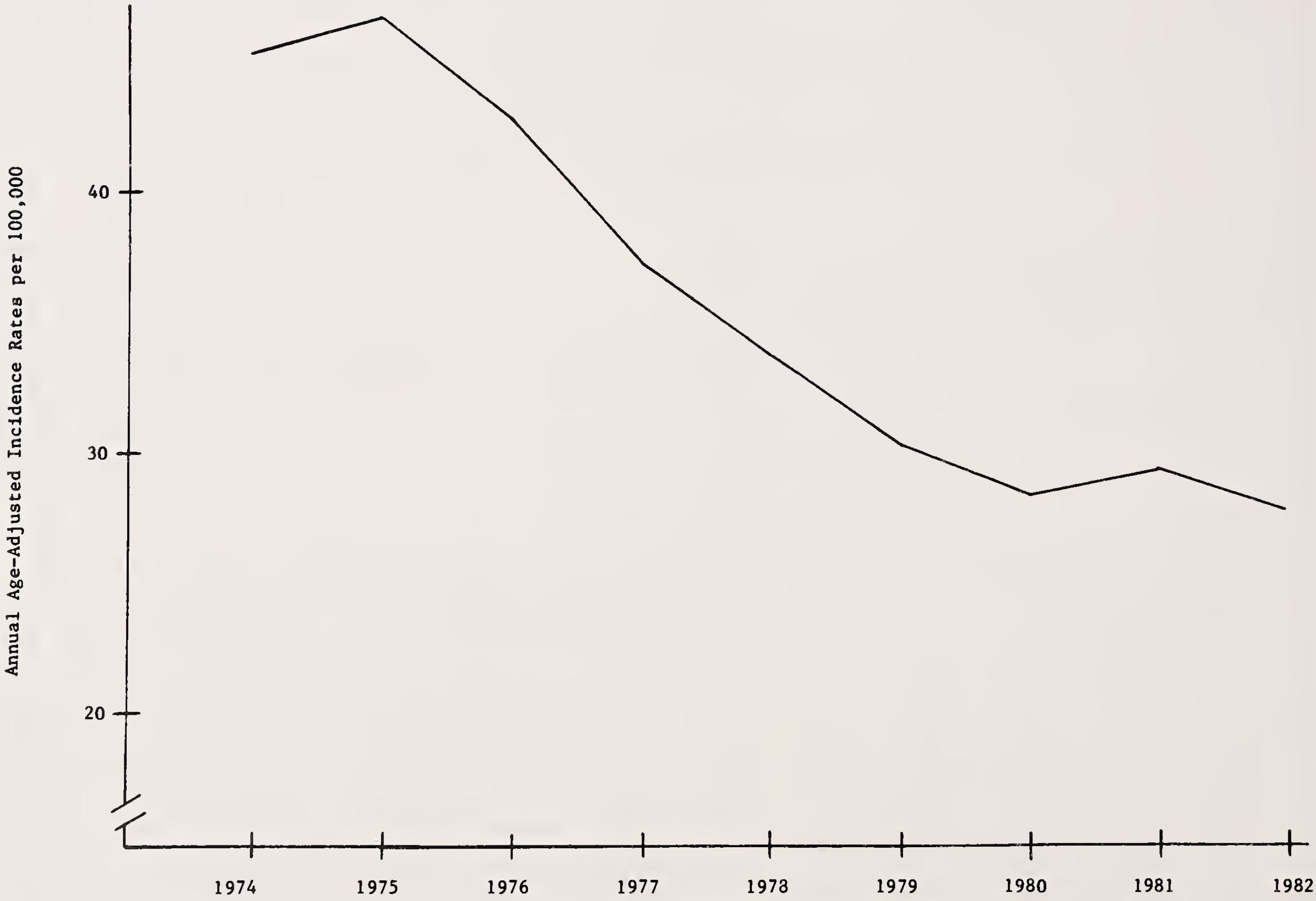

FIGURE 4.—Time trend of endometrial cancer in western Washington.

TABLE 6.—*Time trends in incidence of cervical cancer in younger and older women in 3 areas of the Pacific Basin*[a]

Yr	Ages 20–39 yr			Ages ≥40 yr		
	New Zealand	Alameda	Hawaii	New Zealand	Alameda	Hawaii
1960–66	7.7	17.4	9.8	36.6	40.6	41.3
1967–73	5.8	8.7	8.9	26.0	30.2	32.7
1973–77	9.9	14.3	12.0	25.0	19.4	18.6
	Percent change					
Between 1960–66 and 1967–73	−24.9	−49.9	−8.8	−29.0	−25.6	−20.9
Between 1967–73 and 1973–77	+71.5	+64.1	+35.0	−3.7	−35.7	−43.2

[a] Average annual incidence is per 100,000, age-adjusted to 1970 World Population.

numbers from some geographic areas. Changes in reported incidence over time may be influenced by improvements in diagnostic techniques and accuracy of reporting in some areas. Large geographic and temporal variations in cancer occurrence, however, are probably real.

Large variations in incidence among white populations of the Pacific Basin were observed for the following cancers: lung, bladder, melanoma, prostate, and corpus uteri. Some of these geographic variations may be explained by differences in prevalence of known or suspected risk factors for these cancers. The variations in the incidence of lung cancer are most probably due to variations in cigarette consumption (*5*). Risk of bladder cancer has been found to be associated with tobacco use, certain occupational exposures, and possibly coffee consumption (*6*). The low incidence of bladder cancer found in New Zealand and New South Wales may be partly due to a lower prevalence of exposure to these carcinogens in these areas. An association between latitude and occurrence of malignant melanoma has also been found in other areas of the world (*7*) and probably reflects varying exposure to sunlight. The large differences in incidence of cancer of the corpus uteri probably reflect differences in the use of estrogens for treatment of menopausal symptoms (*8*), which is a strong risk factor for cancer of the endometrium (*9–12*). Less easily explained are the variations found for such cancers as prostate, breast, ovary, and stomach.

Lung cancer incidence markedly increased over time in white women of the Pacific Basin. Cohort analyses of cross-sectional data from other areas of the world show that lung cancer incidence is increasing in young women but decreasing in young men (*13*). Some evidence indicates that the prevalence of cigarette smoking has declined in men at a different rate than in women; it is likely that these trends in tobacco consumption are responsible for the different changes in lung cancer incidence over time in the 2 sexes.

Stomach cancer incidence has declined in Western countries in recent years (*1–3*). The reason for this is unknown, but it may be due to changes in diet over time.

The incidence of melanoma has increased elsewhere (*7*) but to a lesser extent than in New Zealand. It is unclear whether residents of New Zealand experienced increased exposure to sunlight than did persons living in other areas of the world.

The occurrence of breast cancer increased to a greater extent in younger than older women. This phenomenon could be due to increasing exposure to causal agents in young women, such as oral contraceptives (*14*), or to earlier detection in recent years.

The higher incidence of invasive cervical cancer over time also varied with age. Armstrong and Holman (*15*) reported a similar phenomenon in Australian women, in whom a 36% rise in the incidence of cervical cancer was found for those 20–39 years old, whereas the rates decreased or remained stable for older women. A number of reports from different countries have shown that mortality from cancer of the cervix has also increased in young women but declined in older women (*16–18*). This phenomenon could be due to changes in sexual practices or more frequent use of oral contraceptives (*19*).

Due to the decline in use of exogenous estrogens for menopausal symptoms (*20*), the occurrence of cancer of the corpus uteri has decreased steadily in the United States since the late 1970s.

The finding of variations in cancer incidence in white populations of the Pacific Basin indicates some areas for future research. The observation of increased incidence of stomach and rectal cancers and decreased incidence of bladder and lung cancer in New Zealand compared with other areas suggests that the study of these neoplasms in New Zealand may provide etiologic clues. The increasing incidence of melanoma and the geographic variations in its incidence should be investigated for elucidation of etiologic factors and methods of prevention. Because the reason for the increasing incidence of breast and cervical cancer in young women is unknown, further research on these cancers in young women is warranted. Effective methods for cessation of tobacco use should be investigated in all areas of the Pacific Basin, so that means of control of cancers of the lung and other smoking-related neoplasms can be instituted.

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Cancer Incidence in the Islands of the Pacific [1, 2]

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ABSTRACT—The South Pacific Commission Cancer Registry has been operational since 1977, and reasonably complete cancer incidence rates are available for New Caledonia, Fiji, Micronesia, the Cook Islands, and Niue. In addition, less complete reporting is available from American Samoa, Papua New Guinea, and French Polynesia. Cancers of the lung, oral cavity, esophagus, liver, and cervix are potentially preventable but prevalent in many Pacific island countries. Unusually low rates of many cancers were observed in Fiji, the most notable being lung and colon-rectum. Thyroid cancer rates are elevated in some but not all female populations. These and other variations in cancer by site are important areas for further research. — Natl Cancer Inst Monogr 69: 73–81, 1985.

One of our specific objectives in conducting this series of Symposia has been to stimulate the collection of descriptive cancer incidence data from the countries bordering on and in the Pacific. The 20 island nations and territories of the Pacific constitute a particularly interesting area in this regard. Most of these countries belong to a confederation, known as the SPC, headquartered in New Caledonia, that attempts to coordinate certain social, health, educational, and economic development programs. The total population of the island nations of the SPC is about 4.5 million and is spread over an area of thousands of square miles, including 500,000 Polynesians, 3,700,000 Melanesians, and 350,000 Micronesians plus smaller numbers of Europeans, Indians, and Asians.

At the first of these Symposia, Dwayne Reed (*1*) reviewed the available descriptive data on cancer in these Pacific Islands. At that time, only 2 countries had cancer registries, Papua New Guinea and Fiji, and both had incomplete reporting. Reed (*1*) pointed out that variation in cancer patterns was considerable among these islands with even the limited data then available.

Stimulated by this report, one of us (BEH) approached the SPC regarding a voluntary system of cancer registration, and in 1979 the SPC endorsed the proposal. This paper presents a summary of the cancer registry data collected through 1982.

MATERIALS AND METHODS

The cancer registry for the SPC was officially begun in 1979. To ensure easy comparison of data from the different countries, we developed a common registration form, based on the form currently used by the New Zealand Cancer Registry, that allowed for the collection of simple descriptive data (e.g., age, sex, residence, and occupation), histopathology (for coding to the International Classification of Diseases for Oncology), and brief details of the therapeutic modalities used. The form was available in English and French for easy utilization throughout the Pacific Islands. The registration forms ordinarily were completed by local registrars and then forwarded to the University of Southern California in Los Angeles where they were coded, edited, and keypunched.

Because the availability of good histopathology is a prime requisite of cancer registration, we initiated the cancer registration system mainly in those countries with resident pathologists and a fairly well-developed infrastructure for the collection of health statistics. The geographic location and ethnic distribution of the countries served by the South Pacific Cancer Registry are shown in figure 1.

The clinical- and pathology-based cancer registry in Papua New Guinea (*2–4*) has been in existence since 1958. Although the reporting is incomplete, the population is the largest of any of the Pacific Islands. Because this Registry has limited resources, we had the local registry form photocopied and transferred it to the SPC abstract form in Los Angeles to simplify their participation. In this way, 5,026 cancers were registered from 1972 to 1978 (table 1); unfortunately, we have not received more current abstracts.

The country-wide registry in Fiji was begun in 1965, and a summary of the findings for the first 5 years was published (*5*). During an initial survey in 1977, it was clear that the reporting completeness had lapsed in the intervening years. Dr. Singh, appointed government pathologist in 1978, organized a new comprehensive cancer reporting

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ABBREVIATIONS: SPC=South Pacific Commission; PIR=proportional incidence rate(s); UICC=International Union Against Cancer; CNS=central nervous system.

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TABLE 1.—*Cancer registries in the South Pacific region*

Country	Yr	Total No. of cases	Estimated completeness, %
Papua New Guinea	1972–78	5,026	40
New Caledonia	1977–81	1,106	90
American Samoa	1976–81	289	85
Fiji	1979–82	1,006	90
French Polynesia	1979–83	381	50
Micronesia[a]	1980–82	645	80
Cook Islands, Niue	1978–80	103	80

[a] This includes the Federated States of Micronesia, Republic of Palau, Republic of Marshall Islands, and the U.S. Trust Territories of Guam and the Mariana Islands.

scheme using the SPC registry form. During a 3-year period (November 1979–October 1982), a total of 1,006 new cancer cases were abstracted.

The cancer registry in New Caledonia was started in 1978 with the enthusiastic support of the Ministry of Health. All new cancer cases were abstracted from 1977 to 1981; a total of 1,106 cases were collected. Approximately 200 from New Caledonia were obtained from the New South Wales, Australia, Cancer Registry.

The registration scheme in French Polynesia started in 1979 and is less complete than that of New Caledonia.

Cancer registration of American Samoans is complicated by their frequent movement to Hawaii and the west coast of the U.S. Therefore, we obtained abstracts of all newly diagnosed cancer cases in American Samoa (from the pathology files of the L. B. Johnson Tropical Disease Hospital in Pago Pago, American Samoa) or in Los Angeles County and Hawaii (from the records of the population-based cancer registries in these areas).

To collect data from the island groups in Micronesia (Federated States of Micronesia, Republic of Palau, Republic of Marshall Islands, Guam, and the Northern Mariana Islands), a well-trained cancer registrar from the Hawaii Tumor Registry travelled throughout the region in 1983. A total of 629 cancer cases were obtained retrospectively covering the period January 1, 1980 to December 1982. Others were taken from the Hawaii Tumor Registry.

Cases from Niue and the Cook Islands were obtained from the New Zealand Cancer Registry as Niue has a small population (5,000) and is geographically and culturally close to the Cook Islands. The data from these 2 island nations are combined. Virtually all cancer patients from these islands are referred to New Zealand for therapy. From 1978 to 1980, 103 cases were added to the files.

RESULTS

For those cancer registries listed in table 1 for which the estimated completeness of reporting exceeds 75%, site-specific incidence rates were calculated with the use of current population estimates supplied by the SPC and are presented in tables 2 and 3 (*6*). These estimates included age, sex, and ethnic data for New Caledonia, Fiji, the Cook Islands, and Niue. Current estimates of the population of Micronesia by ethnic group are not available, so incidence rates were calculated for all races combined. Cancer incidence rates for the Polynesian population of Hawaii and New Zealand were given for comparison.

For the countries for which complete case reporting (more than 75%) is not available (Papua New Guinea, French Polynesia) or satisfactory denominators are not available as in American Samoa, PIR (*7*) were calculated with the Los Angeles County European population as a basis for comparison (tables 4, 5). In addition, the cancer cases from Micronesia were separated into those occurring in Micronesians and those occurring in Chamorros (the native population of Guam), and PIR were calculated separately for these 2 ethnic groups. The results of these analyses must be interpreted cautiously, however, because such proportional rates can easily lead to misleading impressions regarding true increases or decreases in incidence.

Polynesians

In a previous paper, we (*8*) presented the available data on cancer by site for the Polynesians of Hawaii, New Zealand, and American Samoa. The cancer patterns of these geographically widely separated populations were remarkably similar but quite different from those of the European migrants living in those areas.

In tables 2 and 3, the Polynesians from Hawaii and New Zealand show high rates of neoplasms of the stomach, pancreas, lung, breast, and prostate compared with the Micronesian and Melanesian populations. With even small numbers of cases for comparison, the Polynesians of Cook Islands and Niue also have high rates of lung, stomach, and breast cancers. In common with the Melanesian and Micronesian populations, Polynesians uniformly have high rates of liver cancer, particularly males. The American Samoans and French Polynesians have a similar pattern (except for breast cancer) based on PIR (tables 4 and 5). Male Hawaiian Polynesians and possibly French Polynesians have elevated rates of cancer of the esophagus, and male and female Polynesians from Hawaii and female Polynesians from American Samoa, Niue, and the Cook Islands have elevated rates of thyroid cancer. However, these differences in cancers of the esophagus and thyroid are not unique to the Polynesians among the island populations.

Melanesians

In contrast to the remarkably similar pattern of cancer among the Polynesians, the type and frequency of cancer among the 3 Melanesian populations of Papua New Guinea, Fiji, and New Caledonia are dissimilar.

Fiji

Cancer incidence in the Fijian Melanesians is low. Rates for stomach, breast, lung, and prostate cancers are considerably below those of the Polynesians; those for liver, cervix, and ovaries are generally similar to those of the Polynesians.

The Indians, who originally came to Fiji as indentured servants between 1879 and 1916, have about the same total population size as the native Fijian Melanesians (fig. 1). Their cancer rates also are low. Among the common sites

TABLE 2.—*Age-adjusted incidence rates for cancer in Pacific Island males*[a]

Site/type	Micronesia		Fiji				New Caledonia				Cook Islanders/Niue		New Zealand[b]		Hawaii[b]	
	All races		Melanesians		Indians		Melanesians		Europeans		Polynesians		Polynesians (Maoris)		Polynesians	
	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases
Oropharynx	10.3	20	2.1	6	4.1	7	14.0	14	25.5	24	10.6	2	6.3	12	8.9	13
Esophagus	3.8	7	1.8	4	1.4	3	12.5	10	13.2	11	10.6	2	6.1	9	11.2	17
Larynx	4.5	9	0.3	1	3.2	5	3.4	4	5.1	6	—	0	5.0	8	5.6	8
Lung	46.7	89	5.5	12	2.0	4	34.3	31	50.9	48	71.1	15	110.4	176	94.6	134
Bladder	2.1	4	0.4	1	5.0	8	5.1	4	8.4	8	9.6	2	4.2	8	10.6	15
Kidney	0.9	2	1.1	3	0.8	1	0.7	1	0.9	1	—	0	7.0	14	7.2	11
Stomach	6.6	13	7.7	17	3.9	7	15.6	13	12.3	12	24.0	5	33.7	49	40.2	52
Colon	7.9	18	4.5	11	2.7	5	5.6	6	14.0	11	15.9	3	10.4	21	24.7	35
Rectum	7.6	14	2.8	7	1.8	4	2.3	2	12.8	13	—	0	12.7	20	17.4	26
Liver	11.4	22	9.3	20	0.4	1	16.4	16	7.5	7	14.5	4	11.8	21	6.7	9
Pancreas	5.5	10	0.5	1	0.8	1	3.5	3	3.7	4	4.3	1	12.9	22	8.7	13
Breast	0.9	2	1.1	2	—	0	—	0	—	0	5.3	1	2.3	3	—	0
Prostate	12.4	21	5.0	10	4.7	6	3.7	3	24.4	19	15.9	3	36.5	47	40.8	48
Testes	1.3	4	0.9	3	0.6	3	1.4	2	5.7	8	—	0	7.6	27	2.9	7
Penis	1.2	2	—	0	0.8	1	1.4	1	—	0	—	0	1.6	2	0.7	1
Thyroid	—	0	1.1	2	0.4	1	0.7	1	0.7	1	—	0	2.7	6	7.3	13
Bone	1.2	4	1.5	6	—	0	1.3	2	0.8	1	—	0	0.7	4	0.9	2
Connective tissue	2.9	6	4.1	11	1.6	2	—	0	0.8	1	1.9	1	2.1	9	5.6	7
Melanoma	1.0	3	1.9	5	0.4	1	—	0	9.7	11	—	0	1.8	4	0.8	2
CNS	3.5	10	1.7	5	0.8	3	2.1	3	2.1	3	—	0	12.2	31	4.3	10
Leukemia	6.7	18	2.2	9	4.2	13	7.3	10	6.4	6	—	0	11.1	29	9.4	20
Lymphoma	3.6	8	3.4	11	1.8	7	1.8	3	2.2	2	5.3	1	6.7	14	8.9	14
Hodgkin's lymphoma	1.6	4	1.6	5	1.4	5	0.5	1	—	0	—	0	3.9	9	1.0	3
Myeloma	1.0	2	2.1	4	—	0	1.4	1	1.4	1	13.8	3	6.7	10	5.9	8

[a] Rates are age-adjusted per 100,000 population.

[b] Cancer registry data for Hawaii and New Zealand are presented for comparison.

TABLE 3.—*Age-adjusted incidence rates for cancer in Pacific Island females*[a]

Site/type	Micronesia		Fiji				New Caledonia				Cook Islanders/Niue		New Zealand[b]		Hawaii[b]	
	All races		Melanesians		Indians		Melanesians		Europeans		Polynesians		Maoris		Polynesians	
	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases
Oropharynx	6.0	12	1.6	4	0.7	2	5.2	4	7.3	7	—	0	3.0	7	6.5	12
Esophagus	—	0	—	0	3.0	5	—	0	—	0	—	0	0.7	1	1.3	3
Larynx	—	0	—	0	—	0	0.9	1	—	0	5.0	1	0.7	2	2.7	4
Lung	13.4	25	1.4	3	1.3	2	14.2	12	7.2	6	4.7	1	80.7	131	28.6	46
Bladder	1.6	3	0.5	1	0.9	1	6.1	5	1.1	1	—	0	5.7	8	5.3	8
Kidney	2.1	5	1.5	4	1.8	4	—	0	0.7	1	—	0	2.8	6	1.7	3
Stomach	3.6	7	2.0	5	5.3	10	6.8	6	6.1	5	14.6	3	20.3	38	17.8	30
Colon	8.0	15	2.0	6	2.5	4	—	0	8.3	7	5.0	1	13.6	25	11.3	19
Rectum	4.4	8	3.1	9	1.1	2	2.3	2	4.7	4	4.7	1	5.3	9	8.0	12
Liver	1.8	4	5.1	13	0.4	2	6.3	6	—	0	9.6	2	4.2	7	2.9	5
Pancreas	1.6	3	1.0	2	2.3	3	5.2	4	2.5	2	—	0	5.1	9	8.3	14
Breast	21.6	41	20.1	53	20.9	44	16.6	18	43.3	39	45.3	10	61.4	129	95.0	164
Cervix	18.4	39	34.1	94	34.8	81	31.5	37	18.2	18	23.6	5	42.2	114	21.4	48
Ovary	4.0	9	11.7	31	5.5	11	4.3	5	7.6	7	8.6	2	12.4	30	8.6	16
Thyroid	5.9	12	3.6	10	2.9	7	10.7	10	6.4	6	18.6	4	2.5	6	9.3	19
Bone	—	0	1.0	3	0.4	2	2.1	3	—	0	—	0	2.1	3	2.0	6
Connective tissue	2.3	5	1.9	5	1.7	5	—	0	—	0	9.9	2	2.5	6	0.6	2
Melanoma	1.9	5	0.6	2	—	0	—	0	4.2	4	5.0	1	0.8	3	1.9	5
CNS	2.0	7	—	0	—	0	2.5	3	1.8	2	5.0	1	5.6	17	2.5	6
Leukemia	2.6	9	1.1	4	3.5	11	2.4	4	2.2	2	12.8	3	5.8	15	3.7	7
Lymphoma	1.4	4	1.3	3	0.6	3	1.4	1	2.0	2	—	0	3.9	11	4.4	8
Hodgkin's lymphoma	0.8	2	0.3	1	0.6	2	—	0	1.6	2	—	0	1.0	3	—	0
Myeloma	1.2	2	—	0	3.6	4	—	0	—	0	—	0	6.4	11	3.8	6

[a] Rates are per 100,000 population.

[b] Cancer registry data for Hawaii and New Zealand are presented for comparison.

TABLE 4.—*PIR for cancer in Pacific Island males*[a]

Site/type	Papua New Guinea (Melanesians)				Micronesia				American Samoa		Tahiti	
	Highlanders		Lowlanders		Micronesians		Chamorros		Polynesians		Polynesians	
	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases
Oropharynx	100	57	287	388	110	11	98	6	59	7	96	8
Esophagus	83	2	493	32	—	0	447	4	67	1	201	2
Larynx	25	3	143	43	84	3	120	3	23	1	139	4
Lung	14	12	11	25	156	41	131	24	101	32	177	38
Bladder	27	9	11	9	11	1	17	1	29	3	14	1
Kidney	34	7	11	6	—	0	—	0	21	1	27	1
Stomach	234	29	164	52	84	3	163	4	211	9	206	6
Colon	56	21	19	18	41	4	61	4	26	3	13	1
Rectum	129	26	29	15	34	2	150	6	58	4	21	1
Liver	4,537	202	1,847	206	1,170	12	959	6	1,065	12	890	8
Pancreas	9	1	15	4	62	2	225	5	104	4	38	1
Breast	341	6	114	5	250	1	379	1	—	0	—	0
Prostate	24	3	16	6	105	11	41	3	216	26	62	5
Testes	2	1	13	12	27	1	123	1	—	0	28	1
Penis	120	2	522	21	287	1	460	1	—	0	—	0
Thyroid	30	6	17	8	—	0	—	0	43	1	—	0
Bone	149	15	177	35	347	4	—	0	75	1	424	4
Connective tissue	156	23	224	74	209	4	235	2	103	2	—	0
Melanoma	37	24	21	32	—	0	—	0	12	1	59	4
CNS	15	7	7	7	122	8	—	0	41	3	34	2
Leukemia	70	27	53	49	78	5	221	7	95	6	144	9
Lymphoma	94	26	176	114	89	4	40	1	158	8	52	2
Hodgkin's lymphoma	23	7	24	15	100	3	—	0	—	0	39	1
Myeloma	—	0	9	1	—	0	240	2	140	2	312	3

[a] All PIR were adjusted to the European migrant population of Los Angeles, California.

shown in tables 2 and 3, the Indian males have the lowest rates of lung, stomach, colon, rectum, liver, and pancreas cancers. Indian females have similarly low rates of most cancers, although their rates of cervix and breast cancers are not substantially different from the Polynesians and Melanesians.

Boyd et al. (*5*) published incidence data for the Fijian Melanesian and Indian populations for 1965–69. They presented the age-adjusted rates by site using the UICC African population standard suggested by Knowelden and Davis (*9*). In table 6 is a comparison between the incidence rates from this earlier period (1966–69) and the more recently derived data (1979–82) age-adjusted to the same African standard population. Compared with the rates of the Birmingham, England, population cited by Boyd et al. (*5*) or to the more current on U.S. natives, or European migrants in Australia and New Zealand (*7*), the total cancer rates for both periods in Fijian and Indian males are low, i.e., less than one-third and one-fourth the European migrant rates, respectively. We have good reason to believe that these low rates cannot be explained by incomplete cancer reporting (*5*). The total cancer rates in females are not as low (e.g., in comparison they are perhaps one-half the rates of all cancers in the U.S. or Australian and New Zealand European migrant women). This is primarily because of the higher rate of cervix cancer in the Fijian women.

When comparing the 2 periods, one sees little change in the cancer incidence rates among the Melanesians and Indians, with four notable exceptions: a decrease in stomach cancer in all but Indian females, a substantial increase in colon-rectum cancer among Melanesian males and females, and increases in breast and cervix cancers in both female populations. The increase in cervix cancer is probably at least partially an artifact as a relatively complete cervix cancer screening program was conducted throughout Fiji in 1980–81 (during the period covered by the current cancer registration scheme). In both periods, the Melanesian males had substantially higher liver cancer rates than did their Indian counterparts. In the earlier period, the incidence of thyroid cancer in Melanesian women was much higher than that in the Indian women, but, in the second period, the rates were almost identical.

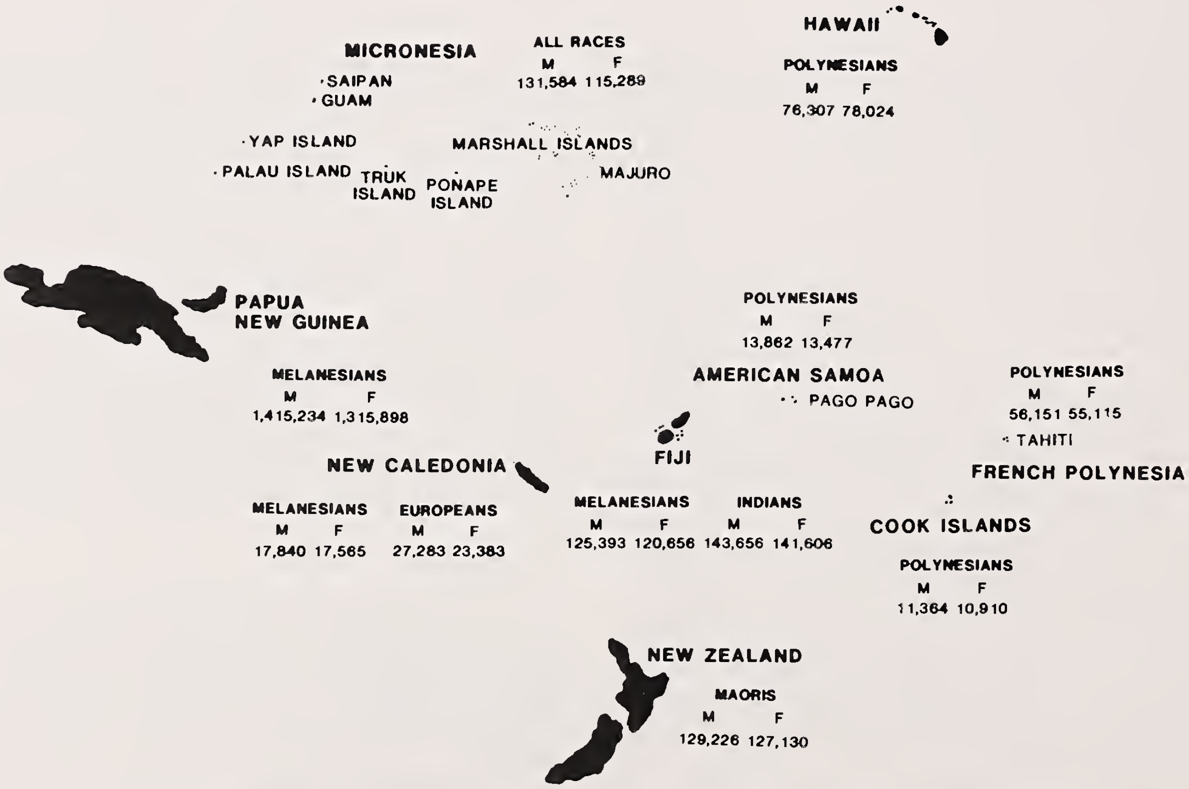
New Caledonia

The Melanesians of New Caledonia have substantially higher rates of cancer of many sites than do their Fijian counterparts (tables 2 and 3). This difference is most notable in males and for cancers of the oropharynx, esophagus, larynx, lung, stomach, liver, and pancreas, and leukemia. With regard to these same cancers, the Melanesian males of New Caledonia have rates similar to male European migrants who have, in addition, higher rates

TABLE 5.— *PIR for cancer in Pacific Island females*[a]

Site/type	Papua New Guinea (Melanesians)				Micronesia				American Samoa		Tahiti	
	Highlanders		Lowlanders		Micronesians		Chamorros		Polynesians		Polynesians	
	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases	Rates	No. of cases
Oropharynx	91	21	399	169	170	7	100	3	138	6	61	3
Esophagus	—	0	318	6	—	0	—	0	—	0	222	1
Larynx	61	1	165	5	—	0	—	0	—	0	348	2
Lung	6	2	14	8	154	12	138	9	114	10	119	12
Bladder	—	0	22	2	73	1	—	0	—	0	—	0
Kidney	61	5	41	6	258	4	113	1	62	1	—	0
Stomach	560	22	243	18	193	2	348	3	796	9	564	7
Colon	13	3	33	14	52	3	177	8	50	3	15	1
Rectum	141	13	77	13	126	3	96	2	110	3	33	1
Liver	1,760	52	933	55	310	2	—	0	603	3	855	5
Pancreas	—	0	12	1	79	1	178	2	209	3	63	1
Breast	35	60	27	82	34	10	78	16	69	22	74	29
Cervix	76	127	68	207	150	24	33	4	63	12	149	30
Ovary	411	123	263	143	18	1	80	3	106	6	119	8
Thyroid	26	6	46	19	234	7	54	1	168	5	205	7
Bone	397	17	277	29	—	0	—	0	406	3	—	0
Connective tissue	215	24	217	48	176	4	—	0	241	4	93	2
Melanoma	53	18	39	24	23	1	34	1	—	0	—	0
CNS	53	13	10	5	58	3	—	0	62	3	60	3
Leukemia	59	13	55	23	183	8	—	0	87	3	105	5
Lymphoma	149	16	230	47	168	4	—	0	135	3	117	3
Hodgkin's lymphoma	22	2	28	5	54	1	—	0	—	0	159	2
Myeloma	—	0	—	0	—	0	277	1	—	0	411	2

[a] All PIR were adjusted to the European migrant population of Los Angeles, California.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COOK ISLANDS
POLYNESIANS
M F
11,364 10,910
NEW ZEALAND
MAORIS
M F
129,226 127,130

FIGURE 1.—Location and population characteristics of South Pacific Cancer Registry participants.

TABLE 6.—*Cancer incidence in Fiji for 1966–69 and 1979–82*[a]

Site/type	Males				Females			
	Indians		Melanesians		Indians		Melanesians	
	1966–69	1979–82	1966–69	1979–82	1966–69	1979–82	1966–69	1979–82
Mouth, pharynx	1.8	2.1	1.0	1.9	1.3	0.5	0.8	1.1
Esophagus	1.2	0.8	1.8	1.0	0.3	1.7	0.3	0.0
Stomach	4.3	2.2	6.1	4.3	3.1	3.2	2.8	1.3
Colon/rectum	3.2	2.9	1.4	5.0	2.6	2.3	2.1	4.5
Liver	0.2	0.3	3.9	5.1	1.3	0.6	1.1	3.3
Larynx, lung	4.6	2.7	5.8	3.6	1.0	0.7	3.0	0.8
Prostate	2.1	2.2	3.1	2.4	—	—	—	—
CNS	1.0	0.7	1.6	1.4	0.7	0.0	1.4	0.0
Bladder/kidney	0.6	3.1	1.2	0.9	0.1	1.5	0.9	1.2
Thyroid	0.6	0.3	0.3	0.5	0.8	2.1	5.6	2.9
Lymphoma	2.9	3.0	1.6	5.1	2.9	1.3	1.7	1.1
Leukemia	1.8	3.2	2.7	2.2	2.1	2.8	3.0	1.0
Breast	—	—	—	—	4.1	14.4	11.7	15.4
Cervix	—	—	—	—	19.0	25.3	19.4	29.1
Ovary	—	—	—	—	4.5	3.5	3.6	8.5
Total[b]	34.4	31.9	48.0	54.2	61.2	85.6	72.5	94.8

[a] Rates are age-adjuted to the UICC Africa Standard.

[b] Totals given are for all sites studied, not just for those listed.

of colon, rectum, prostate, and testis cancers than do the Melanesians and substantially higher rates of melanoma than any of the island populations in the tables.

Melanesian females of New Caledonia also have higher rates of cancers of the oropharynx, lung, stomach, pancreas, and thyroid than do Fijian women. The female European natives now in New Caledonia have higher rates of melanoma and cancers of the colon–rectum and breast and lower rates of cervix cancer than do Melanesian females.

Some interesting differences are seen between the cancer patterns in the Melanesians of New Caledonia and the Polynesians. The Polynesians have still higher rates of lung, stomach, colon–rectum, pancreas, prostate, and breast cancers than do the Melanesians. However, with the exception of Hawaiian and perhaps Tahitian males, the other Polynesian populations do not have such high rates of neoplasms of the oropharynx and esophagus.

Papua New Guinea

The pattern of cancer in New Guinea Melanesians has been presented before (*3, 4*). In tables 4 and 5, the Melanesians are divided into those who live in the highlands and lowlands along the coast, or on the Islands of New Britain, New Ireland, Bougainville, and Manus. The lowlanders have higher PIR for oral cancer that have been related to betel nut use, and for lymphoma, particularly the Burkitt type, that has been correlated with malaria (*3*). In addition to these tumors, the lowlanders also have higher PIR for thyroid cancer (females only) and cancers of the esophagus, larynx, and penis than do the highlanders. The apparent excess of stomach and liver cancers in the highlanders essentially disappears after adjustment for the excess in the lowlanders (*3*). Cancers of the lung, colon, pancreas, prostate, testis, and thyroid have low PIR in lowlanders and highlanders, and except for thyroid cancer, among the Melanesians of Fiji (tables 2, 3).

Micronesians

The cancer rates for Micronesia listed in tables 2 and 3 include all races because age and race-specific denominators are not available for the 4 territories of the area known as Micronesia. The pattern of cancer in Micronesia is generally similar to that of the Polynesians and the Melanesians of New Caledonia in showing elevated rates of cancers of the oropharynx, larynx, lung, liver, pancreas, and leukemia. Unlike the Polynesians, the rates of stomach, breast, and prostate cancers are not high.

Like the Polynesians and Melanesians, the Micronesians have higher rates of liver and cervix cancer and lower rates of that for the colon–rectum in males and melanoma in both sexes than European migrants to New Caledonia or elsewhere in the Pacific (*7*).

The PIR for the Micronesians compared with the Chamorros are shown in tables 4 and 5. The number of cases is small, but if both sexes are considered a relative excess is apparent of stomach, colon–rectum, and pancreas cancers among Chamorros and of cervix, thyroid (females), CNS tumors, and lymphomas in the Micronesians.

DISCUSSION

We encountered some obvious difficulties in attempting to obtain good descriptive cancer data on populations scattered across the Pacific Islands. Some of the island populations are small, and, therefore, cancer incidence data are subject to considerable inaccuracies and limitations unless data collection continues for longer than we have done to date. Such is clearly the situation for the Cook Islands, Niue, and the separate countries and territories of

Micronesia. In addition, complete collection of cancer cases is not possible in certain areas such as Papua New Guinea. Finally, standardization of procedures for systematic collection of cancer data, even in those areas where the medical care infrastructure makes the task feasible, is difficult because of varying systems of medical care, culture, and language.

Nevertheless, the cancer data that have been collected so far do provide for some meaningful comparisons between islands and ethnic groups. From these comparisons, we can at this stage draw some general conclusions about the cancer problems in the Pacific Islands.

Undoubtedly, cigarette smoking and betel nut chewing constitute the 2 most readily preventable cancer risk factors for the Pacific Islands. Lung cancer accounts for 25–30% of all cancer in males and 10–15% in females. The cigarette-smoking habits of Polynesians in Hawaii and New Zealand are known to be similar to or even exceed those of the European populations in the same areas (*8*). However, lung cancer appears to be in excess beyond that explainable just on the basis of current smoking habits, which may be due to smoking begun at an earlier age, greater inhalation, or perhaps a low vitamin A intake (*8*). To our knowledge, no one has published data on the frequency of cigarette smoking in Polynesians in American Samoa and French Polynesia, Micronesians, or Melanesians from New Caledonia; however, simple observation would suggest that these people also smoke frequently enough to explain their excess lung cancer.

Betel nut chewing is strongly associated with oral cancer in Papua New Guinea (*2-4*). This cancer accounts for 20 and 33% of all cancer in females and males, respectively, from the lowlands where the *Areca catechu* palm nut grows. Unlike those who practice the habit in India, the chewers of Papua New Guinea usually do not use tobacco in the quid, and it is still not clear whether the primary cause of cancer is the betel nut or the slake lime that is commonly used at the same time. A recent study in the Solomon Islands found the highest risk of oral cancer in betel nut users who regularly used lime (*10*). The practice of betel nut chewing can be found in Guam and certain other areas of Micronesia as well and most likely accounts for some portion of cancer in those areas.

One additional unstudied issue related to betel nut chewing is whether this practice is associated also with esophageal cancer. In Papua New Guinea, the lowlanders have a considerable excess risk of esophageal as well as oral cancer, and within the lowlands the highest rates of both overlap. Excesses of esophageal cancer are found also in the Melanesian males of New Caledonia and the Polynesian males of Hawaii and French Polynesia. Previously, we discussed the possibility that these elevated rates in Hawaiians are due to alcohol, particularly beer (*8*). The higher rates in the Melanesians of New Caledonia and French Polynesians could be due to an increased intake of alcoholic beverages, particularly wine, because the latter 2 countries are former French colonies. Migrant Europeans of New Caledonia also have elevated rates of esophageal cancer compared with those of New Zealand, Australia, and the western U.S. (*7*). If alcoholic beverage intake does indeed explain these excess risks of esophageal cancer, then this is a third preventable cause in the Pacific Islands.

A fourth cancer that is increasingly likely to be preventable is that of the liver which accounts for about 10% of all cancers in the Pacific Islanders. Hepatitis B virus has been shown to be a major cause of this cancer in Africa and Asia, although the role of aflatoxin in these areas also needs to be clarified. Of the patients with liver cancer in Papua New Guinea, 82% were positive for hepatitis B-associated antigen (*11*). In Fiji, the higher rates of liver cancer in the Melanesians are correlated with a higher frequency of hepatitis B virus antigenemia compared with the Indians of the same country (*12*). Now that effective vaccines against this virus are available and protection to high-risk infants is feasible, most of these cancers should ultimately be prevented.

Other preventable cancers include those of the oropharynx, larynx, bladder, kidney, and pancreas that are attributable to cigarette smoking. Thus the elevated rates of cancer of the pancreas in the Polynesian and Micronesian populations are likely to be partially the result of cigarette use. It is also likely that stomach cancer rates will continue to fall in the Polynesians as they have elsewhere in the world, whether due to changes in food preservation techniques or the type and amount of foods consumed (*8*). Finally, systematic screening for cancer of the cervix in susceptible populations should at least reduce the mortality from this cancer so common among women in the Pacific island countries.

Control of cigarette smoking, alcohol consumption, and betel nut chewing, vaccination against hepatitis B virus, and early detection and treatment of cervical cancer could lead to a large reduction in mortality in the Pacific Islanders. Although these goals may not be easily achieved, they do demonstrate that control of cancer is possible in this area.

Besides the potential for effective prevention based largely on feasible public health intervention strategies, the data from the SPC Registry suggest important areas for research. Perhaps most intriguing is the low rate of many cancers among the Melanesians and Indians of Fiji, notably the low rates of lung cancer in men. These rates in Fijian and Indian males are one-fourth or less than those of the Polynesians and Micronesians. It is unlikely that differences in current cigarette-smoking practices can account for this, as more than 80% of Melanesian and 50% of Indian men are current smokers (*13*). Perhaps regular smoking of cigarettes was adopted earlier and more extensively outside of Fiji but no published data support or refute this contention. An alternative explanation is that the Fijian population is partly protected against the harmful effects of cigarette smoke because of their dietary consumption of certain vitamins and trace elements. It is known that the Fijian Melanesian and Indian populations consume large quantities of dark, leafy green vegetables such as bele (*Hibiscus esculartus*) and rourou (taro leaf), both of which contain high concentrations of vitamin A precursors (*14*).

The generally low rates of colon cancer among many of the island populations also is deserving of further investigation. Dietary fiber intake may be higher in these populations than in current European or U.S. populations, but this fact has not been well documented. Other worthy areas for research include studies of the high frequency of thyroid cancer in certain island populations (New Caledonia, Cook Islands, Niue, and Hawaii) and the high rates of stomach, breast, and lung cancer in the Polynesians (*8*).

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Cancer Incidence in Japanese in Japan, Hawaii, and Western United States [1, 2]

Suketami Tominaga [3, 4]

ABSTRACT—We based our systematic review of the cancer incidence rates of 48 anatomic sites of Japanese in Japan (Miyagi, Osaka, and Fukuoka Prefectures) and Japanese and Caucasians in the United States (Hawaii, San Francisco Bay Area, and Los Angeles County) on the cancer incidence data included in volume IV of "Cancer Incidence in Five Continents." Cancer sites were classified into 10 categories according to the trend of cancer incidence among the 3 groups. To evaluate the influences of environmental and racial factors, we used the ratio of cancer incidence in Japanese living in the United States to that of native Japanese, and the ratio of cancer incidence in Caucasians to that of Japanese living in the same areas of the United States. The present study revealed that the risks of cancers of the prostate, corpus uteri, colon, thyroid, breast, ovary, and testis were elevated, whereas those of the stomach, esophagus, and cervix uteri were decreased in the United States. Caucasians were more susceptible to melanoma, cancers of the mouth, lip and vermilion border, tongue, oropharynx, and larynx than were the Japanese, but the Japanese were more susceptible to cancers of the stomach, gallbladder, and liver. The difficulties we encountered in differentiating the influences of environmental factors from those of genetic racial factors are discussed. The necessity for further observations of the life-style (especially dietary habits) and the cancer incidence of Japanese living in the United States and comparisons with those of native Japanese and Caucasians are emphasized.—Natl Cancer Inst Monogr 69: 83-92, 1985.

Studies of migrants, which offer some clues to the relative importance of genetic and environmental factors in the etiology of cancer, are useful especially when the differences in mortality or incidence of cancer and life-style are large between the country of origin and the host country. Thus Japanese living in Hawaii and the continental U.S. are regarded as appropriate study subjects. Since the 1950s, numerous researchers (*1-4*) have reviewed the cancer mortality and incidence rates among USJ and compared them with those of JJ and USW.

Smith (*1*) reviewed the cancer mortality among Japanese in Hawaii and the continental United States for 1949-52 and found that USJ had higher death rates than either whites or nonwhites for cancers of the esophagus, stomach, and liver and biliary passage, whereas they had lower death rates for cancers of the intestines, breast, uterus, ovary, prostate, and urinary tract. Buell and Dunn (*2*) subsequently reviewed the cancer mortality for Japanese in California between 1949 and 1962 and confirmed these earlier results. They also compared cancer mortality between migrants (Issei) and their U.S.-born offspring (Nisei) and found that the shift in relative risk of colon cancer was rapid (complete in Issei) and that of female breast cancer was slow, but that of stomach cancer was intermediate. Haenszel and Kurihara (*3*) further reviewed cancer mortality among Japanese in the entire U.S. for 1959-62 to update and extend earlier results. Dunn (*4*) later reviewed cancer incidence among Japanese in the San Francisco Bay Area for 1969-73 and confirmed earlier results based on mortality statistics.

Our purpose in the present study is to review the recent cancer incidence rates of Japanese in Hawaii and the western continental U.S. and compare them with those of JJ and USW for cancers at various sites, including those not studied in previous investigations.

MATERIALS AND METHODS

The cancer incidence data for JJ and Japanese and whites in Hawaii and the western continental U.S. were derived exclusively from (*5*), which includes cancer incidence data from the population-based cancer registries of Miyagi, Osaka, and Fukuoka Prefectures and Nagasaki City in Japan and of Hawaii, Los Angeles County, and the San Francisco Bay Area in the U.S. for the years around 1975. For the 3 cancer registries in the United States, cancer incidence rates were calculated for several ethnic groups including Japanese and Caucasians. In this report, I have excluded cancer incidence data of the Nagasaki Cancer Registry to avoid the possible effects of atomic bomb radiation on incidence rates in Japan. A map of Japan and the U.S. that indicates the cancer registry areas is shown in figure 1.

The size of the population, the years of observation, and the number of cancer patients registered for each study group are shown in table 1. Age-adjusted incidence rates (adjusted to the World Population) of cancer of 48 anatomic sites for each of the 6 cancer registries in Japan and the U.S. were compared, but, generally, the rates were not much different within each country. To obtain more representative rates for each country and ethnic group, I calculated unweighted arithmetic means of the age-ad-

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ABBREVIATIONS: USJ = Japanese living in the United States; JJ = Japanese living in Japan; USW = Caucasians living in the United States; ICD = International Classification of Diseases, Injuries, and Causes of Death, Eighth Revision.

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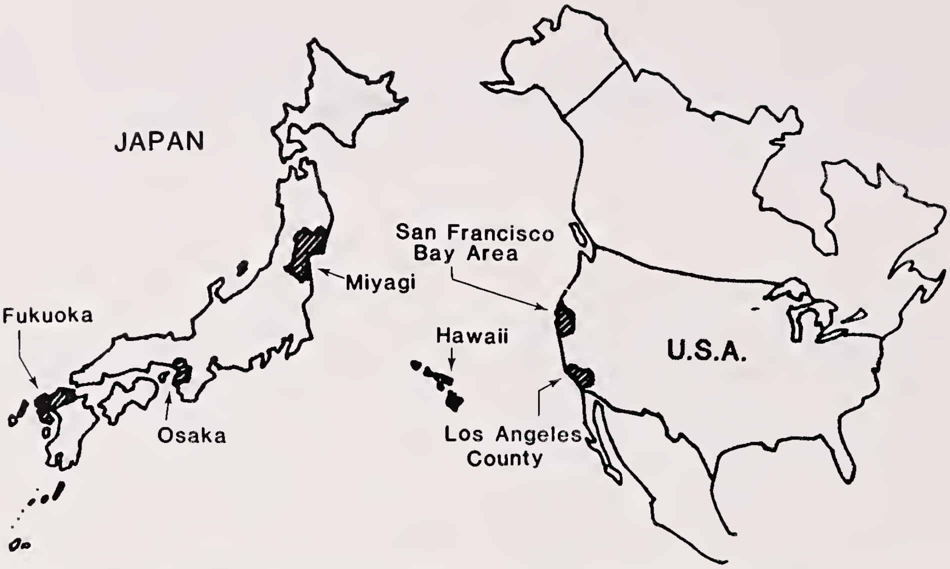

FIGURE 1.—Maps of Japan and the U.S. with cancer registry areas indicated.

justed cancer incidence rates for the 3 cancer registries in Japan and those in the U.S. Statistical tests were not applied to those unweighted arithmetic means because of technical difficulties.

RESULTS

Table 2 shows the average age-adjusted incidence rates of JJ, USJ, and USW for cancer of 48 sites and for all sites combined for the years shown in table 1. The relative cancer incidence rates (the rate fixed for JJ to 1.0) for selected sites for JJ, USJ, and USW are shown in figure 2.

From the results in table 2 and figure 2, the sites of cancer can be classified into 10 categories (types 1–10) according to the relative rates of the 3 groups (fig. 3). Types 1–5 are the sites of cancer for which USW have higher rates than JJ, whereas types 6–10 are the sites of cancer for which USW have lower rates than do the JJ. Types 1 and 6 are the sites of cancer for which USJ have intermediate rates between JJ and USW. Types 2 and 7 are the sites of cancer for which USJ have as high or as low rates as those of USW. Types 3 and 8 are the sites of cancer for which USJ have, respectively, the highest or the lowest rate and USW have intermediate rates between JJ and USJ. Types 4 and 9 are the sites of cancer for which JJ and USJ, respectively, have similar rates and USW have higher or lower rates, respectively, than do JJ and USJ. Types 5 and 10 are the sites for which USJ have the

TABLE 1.—*Size of population, years of observation, and the No. of cancer patients registered for each study group*[a]

Cancer registry	Population		Yr of observation	No. of cancer patients registered[b]	
	Male	Female		Male	Female
Japan					
Miyagi	960,245	995,022	1973–77	9,783	8,152
Osaka	4,132,495	4,146,430	1973–77	33,651	28,525
Fukuoka	2,056,064	2,210,330	1974–75	8,532	7,691
U.S.					
Hawaii					
Japanese	118,932	121,208	1973–77	1,679	1,544
Whites	143,896	121,477	1973–77	1,760	1,629
San Francisco Bay Area					
Japanese	16,892	21,189	1973–77	150	229
Whites	1,239,485	1,290,921	1973–77	23,393	27,238
Los Angeles County					
Japanese	59,690	59,563	1972–77	627	730
Whites	2,401,860	2,533,887	1972–77	50,014	62,330

[a] The census year was 1975 for Japan, Hawaii, and the San Francisco Bay Area, and 1974 for Los Angeles County.

[b] Patients with cancer at all sites including malignant melanoma but excluding other skin cancer were registered.

TABLE 2.—*Comparisons of the cancer incidence rates of JJ, USJ, and USW*

ICD code	Cancer site/type	Age-adjusted incidence rate/100,000 population[a]					
		JJ		USJ		USW	
		Male	Female	Male	Female	Male	Female
140	Lip, vermilion border	0.1	0.0	0.3	0.1	3.6	0.4
141	Tongue	1.0	0.4	0.8	0.5	2.4	1.6
142	Salivary gland	0.4	0.3	0.5	0.6	1.4	0.8
143–5	Mouth	0.9	0.3	0.4	0.5	4.3	2.9
146	Oropharynx	0.2	0.1	0.5	0.4	2.6	1.6
147	Nasopharynx	0.4	0.2	0.8	0.1	0.7	0.2
148	Hypopharynx	0.3	0.1	0.7	0.0	1.7	0.7
150	Esophagus	10.3	2.4	5.6	0.7	3.1	1.7
151	Stomach	80.3	39.6	32.1	18.3	10.8	4.8
152	Small intestine	0.4	0.2	0.9	0.7	0.9	0.5
153	Colon	8.0	6.8	28.3	21.9	27.4	22.1
154	Rectum	8.6	5.6	19.5	8.3	14.8	9.5
155	Liver	5.1	1.4	3.8	1.4	2.5	1.1
156	Gallbladder, etc.	4.3	4.2	3.3	2.8	1.8	1.9
157	Pancreas	6.9	4.0	5.7	4.6	8.7	6.0
160	Nose, sinuses, etc.	1.7	0.9	0.3	0.7	0.7	0.2
161	Larynx	2.7	0.4	2.9	0.3	7.6	1.4
162	Bronchus, trachea, lung	26.6	7.8	32.4	9.6	62.4	23.4
170	Bone	0.9	0.7	0.4	0.4	1.2	0.7
171	Connective tissue	0.6	0.5	1.8	0.8	2.8	1.7
172	Melanoma of skin	0.3	0.3	0.2	0.7	10.1	8.2
173	Other skin	1.2	0.7	—	—	—	—
174	Breast	0.2	15.2	0.2	53.2	0.9	84.9
180	Cervix uteri	—	16.2	—	6.6	—	10.1
181	Chorioepithelioma	—	0.4	—	0.3	—	0.3
182.0	Corpus uteri	—	1.6	—	18.1	—	35.6
183	Ovary, etc.	—	3.3	—	9.7	—	12.6
184	Other female genital	—	0.5	—	0.6	—	2.3
185	Prostate	4.1	—	23.4	—	50.5	—
186	Testis	0.8	—	1.9	—	4.2	—
187.0	Penis	0.3	—	0.2	—	0.5	—
188	Bladder	5.5	1.7	8.5	3.0	22.4	5.2
189	Other urinary	2.4	1.2	4.7	1.3	9.3	3.5
190	Eye	0.3	0.2	0.2	0.0	1.0	0.5
191–2	Brain, nervous system	2.4	1.7	2.5	2.0	6.8	4.3
193	Thyroid	0.9	2.2	3.0	7.0	3.1	6.4
194	Other endocrine	0.4	0.1	0.3	0.2	0.6	0.4
200	Lymphosarcoma, etc.	2.4	1.1	4.9	2.3	5.1	3.7
201	Hodgkin's disease	0.6	0.3	0.7	0.5	3.2	2.2
202	Other reticuloses	1.4	0.8	2.3	1.4	3.9	2.4
203	Multiple myeloma	1.0	0.7	0.8	0.8	2.8	2.2
204	Lymphatic leukemia	0.7	0.6	0.6	1.6	4.1	2.7
205	Myeloid leukemia	2.6	1.7	4.2	1.9	4.3	2.9
206	Monocytic leukemia	0.2	0.2	0.1	0.2	0.1	0.1
207	Other leukemia	1.0	0.8	0.5	0.3	0.8	0.5
208	Polycythemia vera	0.1	0.0	—	—	—	—
209	Myelofibrosis	0.0	0.0	—	—	—	—
—	Other and unspecified	16.5	12.7	6.9	6.1	12.0	8.3
140–209	All sites	205.2	140.3	—	—	—	—
	All sites but 173	204.0	139.5	207.1	190.4	307.0	282.0

[a] Data were adjusted to the World Population.

highest or the lowest rate, respectively, and JJ have intermediate rates between USJ and USW. No sites of cancer fell under type 10.

Table 3 shows the ratios of cancer incidence rates for USJ to those for JJ. The USJ to JJ ratios can be regarded as an index of the influence of environmental factors because both are Japanese. Cancers of the prostate and corpus uteri have the largest such ratios, whereas cancer of the stomach shows a relatively small USJ to JJ ratio in both sexes, which suggest that neoplasms at those sites may be influenced strongly by the environmental factors in the U.S.

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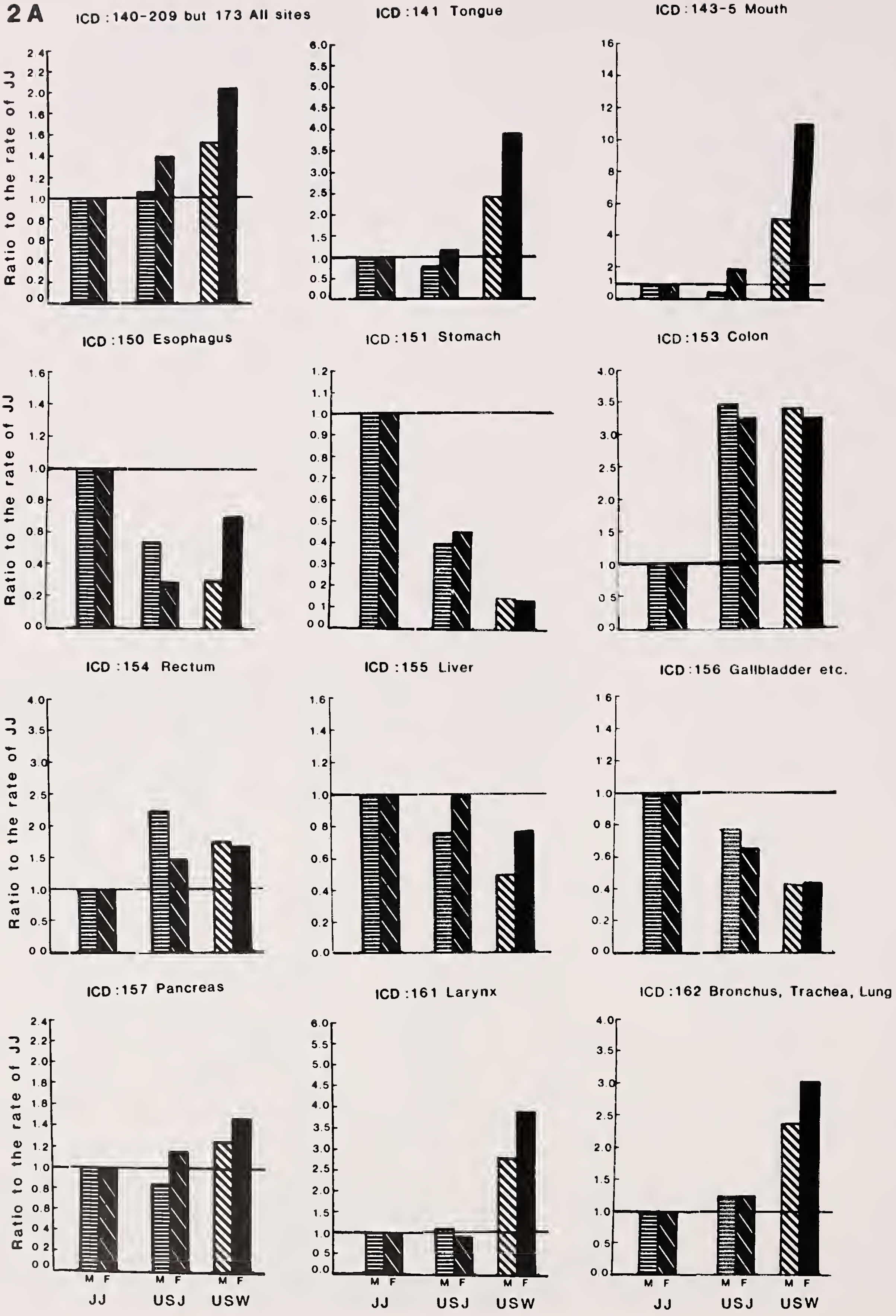

ICD :140-209 but 173 All sites
ICD :141 Tongue
ICD :143-5 Mouth
ICD :150 Esophagus
ICD :151 Stomach
ICD :153 Colon
ICD :154 Rectum
ICD :155 Liver
ICD :156 Gallbladder etc.
ICD :157 Pancreas
ICD :161 Larynx
ICD :162 Bronchus, Trachea, Lung
Ratio to the rate of JJ
M F
JJ
USJ
USW

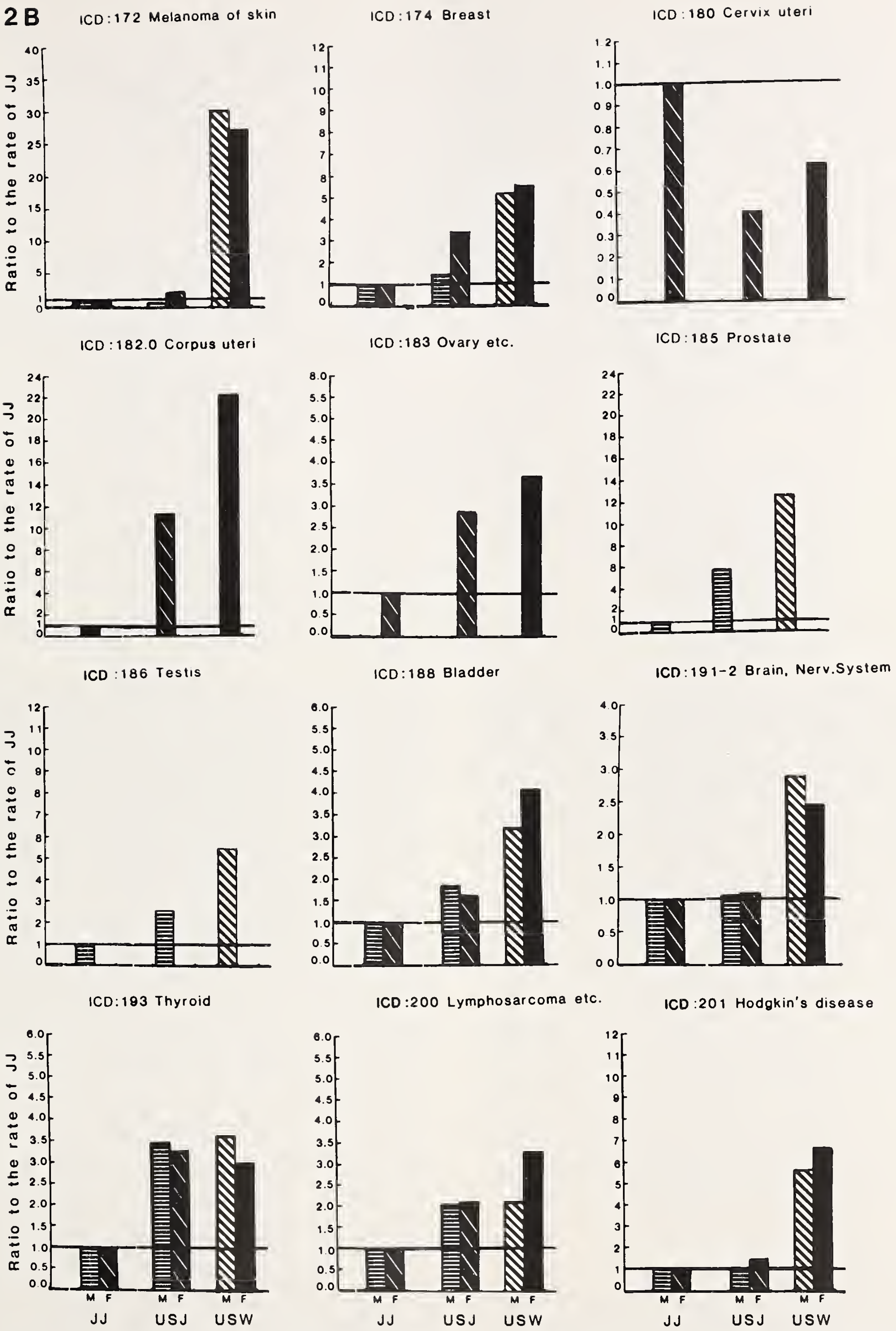
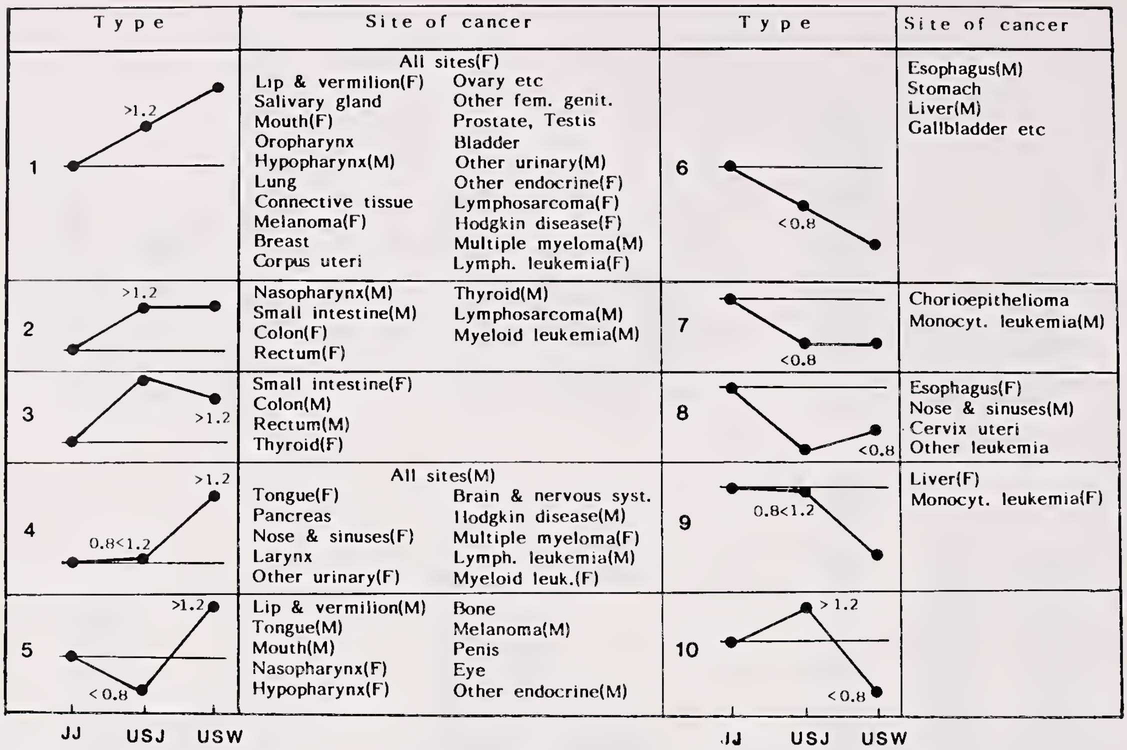


FIGURE 2.—Comparisons of the relative cancer incidence by site among JJ, USJ, and USW. M = male; F = female.



Type	Site of cancer	Type	Site of cancer
1 >1.2	All sites(F) Lip & vermilion(F) Salivary gland Mouth(F) Oropharynx Hypopharynx(M) Lung Connective tissue Melanoma(F) Breast Corpus uteri Ovary etc Other fem. genit. Prostate, Testis Bladder Other urinary(M) Other endocrine(F) Lymphosarcoma(F) Hodgkin disease(F) Multiple myeloma(M) Lymph. leukemia(F)	6 <0.8	Esophagus(M) Stomach Liver(M) Gallbladder etc
2 >1.2	Nasopharynx(M) Small intestine(M) Colon(F) Rectum(F) Thyroid(M) Lymphosarcoma(M) Myeloid leukemia(M)	7 <0.8	Chorioepithelioma Monocyt. leukemia(M)
3 >1.2	Small intestine(F) Colon(M) Rectum(M) Thyroid(F)	8 <0.8	Esophagus(F) Nose & sinuses(M) Cervix uteri Other leukemia
4 >1.2 0.8<1.2	All sites(M) Tongue(F) Pancreas Nose & sinuses(F) Larynx Other urinary(F) Brain & nervous syst. Hodgkin disease(M) Multiple myeloma(F) Lymph. leukemia(M) Myeloid leuk.(F)	9 0.8<1.2	Liver(F) Monocyt. leukemia(F)
5 >1.2 <0.8	Lip & vermilion(M) Tongue(M) Mouth(M) Nasopharynx(F) Hypopharynx(F) Bone Melanoma(M) Penis Eye Other endocrine(M)	10 >1.2 <0.8	

FIGURE 3.—Classification of sites of cancer according to the relative cancer incidence among JJ, USJ, and USW.

The ratios of cancer incidence rates for USW to those for USJ might be regarded as an index of the racial difference in susceptibility to cancer, if one assumes USW and USJ share the same environment (table 4). If USJ have different life-styles from those of USW, the USW to USJ ratio is influenced by racial susceptibility and environmental factors. The USW seem to be far more susceptible to melanoma of the skin and cancers of the mouth, lip and vermilion border, tongue, oropharynx, and larynx than are USJ, but USW seem to be more resistant to cancers of the stomach, gallbladder, and liver than are USJ. However, it is also likely that the life-style, especially eating habits, of USW is more protective for those cancers, especially cancer of the stomach than that of USJ.

The sites of cancer are plotted in figure 4 according to the USJ to JJ ratio and the USW to USJ ratio. The variation in the former ratio (the ordinate) theoretically reflects the influence of environmental difference between the U.S. and Japan, whereas the variation in the latter ratio (the abscissa) theoretically reflects the influence of racial differences between Caucasians and Japanese. However, the influences of environmental and racial differences cannot necessarily be separated clearly by this kind of analysis because it is likely that the life-style of the USJ is still different from that of native Caucasians.

DISCUSSION

Studies of migrants are useful in the determination of the relative importance of environmental factors and genetic factors in the etiology of cancer. Several investigators (*1–4*) have already compared the cancer mortality and incidence rates of USJ with those of native Caucasians and JJ. Previous research was based mostly on the mortality of major sites of cancer. The present study reviews systematically the incidence rates of 48 sites of cancer for JJ in Miyagi, Osaka, and Fukuoka Prefectures and USJ and USW in Hawaii, San Francisco Bay Area, and Los Angeles County. The sites of cancer were classified into 10 categories according to the trend of cancer incidence among those 3 groups. The influences of environmental factors and racial factors were estimated from the ratio of the cancer incidence rate of USJ to that of JJ and the ratio of the cancer incidence rate of Caucasians to that of Japanese living in the same areas of the U.S. The present study revealed that 1) the risks of cancers of the prostate, corpus uteri, colon, thyroid, breast, ovary, and testis were elevated, whereas those of the stomach, esophagus, and cervix uteri were decreased in the U.S., and 2) Caucasians were more susceptible to melanoma, cancers of the mouth, lip and vermilion, tongue, oropharynx, and larynx than were Japanese, but Japanese were more susceptible to cancers of the stomach, gallbladder, and liver. Although the racial difference in the incidence of these sites of cancer may be due partly to the racial differences in the susceptibility to those cancers, it could also reflect the differences in life-style, such as eating habits and sexual behavior. Thus separation of the influence of genetic racial factors from those of environmental factors inherent to each ethnic group is difficult, if based on cancer incidence data alone. Hankin et al. (*6*) and Kolonel et al. (*7, 8*) compared the dietary habits and nutrient intake of Japanese and Caucasians in Hawaii and related them to the incidence of selected sites of cancer. Their studies clearly

TABLE 3.—*Comparisons of the ratios of relative cancer incidence between USJ and JJ*

Male			Female		
ICD code	Cancer site/type	USJ:JJ	ICD code	Cancer site	USJ:JJ
185	Prostate	5.65	182.0	Corpus uteri	11.33
153	Colon	3.53	140	Lip, vermilion border	4.00
193	Thyroid	3.42	146	Oropharynx	3.67
171	Connective tissue	3.24	174	Breast	3.49
186	Testis	2.52	153	Colon	3.24
146	Oropharynx	2.29	193	Thyroid	3.23
154	Rectum	2.25	152	Small intestine	3.00
147	Nasopharynx	2.09	183	Ovary, etc.	2.91
152	Small intestine	2.08	204	Lymphatic leukemia	2.61
200	Lymphosarcoma, etc.	2.01	172	Melanoma of skin	2.44
148	Hypopharynx	2.00	142	Salivary gland	2.25
189	Other urinary	1.97	200	Lymphosarcoma, etc.	2.03
205	Myeloid leukemia	1.64	143–5	Mouth	1.87
202	Other reticuloses	1.58	188	Bladder	1.80
188	Bladder	1.54	202	Other reticuloses	1.71
174	Breast	1.40	171	Connective tissue	1.53
142	Salivary gland	1.27	194	Other endocrine	1.50
162	Lung	1.22	154	Rectum	1.49
201	Hodgkin's disease	1.18	201	Hodgkin's disease	1.40
161	Larynx	1.06	140–209	All sites but 173	1.36
191–2	Brain, nervous system	1.04	162	Lung	1.23
140–209	All sites but 173	1.02	184	Other female genital	1.20
204	Lymphatic leukemia	0.90	203	Multiple myeloma	1.19
157	Pancreas	0.83	141	Tongue	1.17
203	Multiple myeloma	0.81	157	Pancreas	1.15
141	Tongue	0.77	191–2	Brain, nervous system	1.13
156	Gallbladder, etc.	0.77	189	Other urinary	1.09
190	Eye	0.75	205	Myeloid leukemia	1.08
155	Liver	0.75	206	Monocytic leukemia	1.00
172	Melanoma of skin	0.70	155	Liver	0.98
194	Other endocrine	0.67	161	Larynx	0.91
187.0	Penis	0.60	160	Nose, sinuses, etc.	0.85
150	Esophagus	0.55	181	Chorioepithelioma	0.69
207	Other leukemia	0.53	156	Gallbladder, etc.	0.65
206	Monocytic leukemia	0.50	170	Bone	0.65
143–5	Mouth	0.46	147	Nasopharynx	0.60
—	Other and unspecified	0.42	—	Other and unspecified	0.48
170	Bone	0.41	151	Stomach	0.46
151	Stomach	0.40	180	Cervix uteri	0.40
160	Nose, sinuses, etc.	0.18	207	Other leukemia	0.38
140	Lip, vermilion border	0.00	150	Esophagus	0.29
			148	Hypopharynx	0.00
			190	Eye	0.00

TABLE 4.—*Comparisons of the ratios of relative cancer incidence between USW and USJ*

Male			Female		
ICD code	Cancer site/type	USW:USJ	ICD code	Cancer site/type	USW:USJ
140	Lip, vermilion border	(3.6/0.0)	148	Hypopharynx	(0.7/0.0)
172	Melanoma of skin	43.43	190	Eye	(0.5/0.0)
143–5	Mouth	10.75	172	Melanoma of skin	11.18
204	Lymphatic leukemia	6.47	143–5	Mouth	5.73
190	Eye	5.17	201	Hodgkin's disease	4.79
146	Oropharynx	4.88	146	Oropharynx	4.45
201	Hodgkin's disease	4.85	161	Larynx	4.20
174	Breast	3.71	184	Other female genital	3.78
203	Multiple myeloma	3.36	141	Tongue	3.36
170	Bone	3.18	140	Lip, vermilion border	3.25
141	Tongue	3.13	189	Other urinary	2.74
142	Salivary gland	3.07	203	Multiple myeloma	2.60
191–2	Brain, nervous system	2.70	150	Esophagus	2.48
188	Bladder	2.62	162	Lung	2.45
161	Larynx	2.61	147	Nasopharynx	2.33
148	Hypopharynx	2.50	171	Connective tissue	2.22
187.0	Penis	2.33	191–2	Brain, nervous system	2.19
194	Other endocrine	2.25	182.0	Corpus uteri	1.96
160	Nose, sinuses, etc.	2.22	194	Other endocrine	1.83
186	Testis	2.17	202	Other reticuloses	1.76
185	Prostate	2.16	188	Bladder	1.73
189	Other urinary	1.96	204	Lymphatic leukemia	1.70
162	Lung	1.92	170	Bone	1.69
—	Other and unspecified	1.73	200	Lymphosarcoma, etc.	1.61
202	Other reticuloses	1.71	174	Breast	1.60
207	Other leukemia	1.56	205	Myeloid leukemia	1.57
171	Connective tissue	1.53	207	Other leukemia	1.56
157	Pancreas	1.51	180	Cervix uteri	1.53
140–209	All sites but 173	1.48	140–209	All sites but 173	1.48
200	Lymphosarcoma, etc.	1.03	—	Other and unspecified	1.36
193	Thyroid	1.03	157	Pancreas	1.30
205	Myeloid leukemia	1.03	183	Ovary, etc.	1.30
206	Monocytic leukemia	1.00	142	Salivary gland	1.28
153	Colon	0.97	154	Rectum	1.14
152	Small intestine	0.96	153	Colon	1.01
147	Nasopharynx	0.96	181	Chorioepithelioma	1.00
154	Rectum	0.76	193	Thyroid	0.91
155	Liver	0.65	155	Liver	0.79
150	Esophagus	0.55	156	Gallbladder, etc.	0.67
156	Gallbladder, etc.	0.55	152	Small intestine	0.67
151	Stomach	0.34	206	Monocytic leukemia	0.57
			160	Nose, sinuses, etc.	0.32
			151	Stomach	0.26

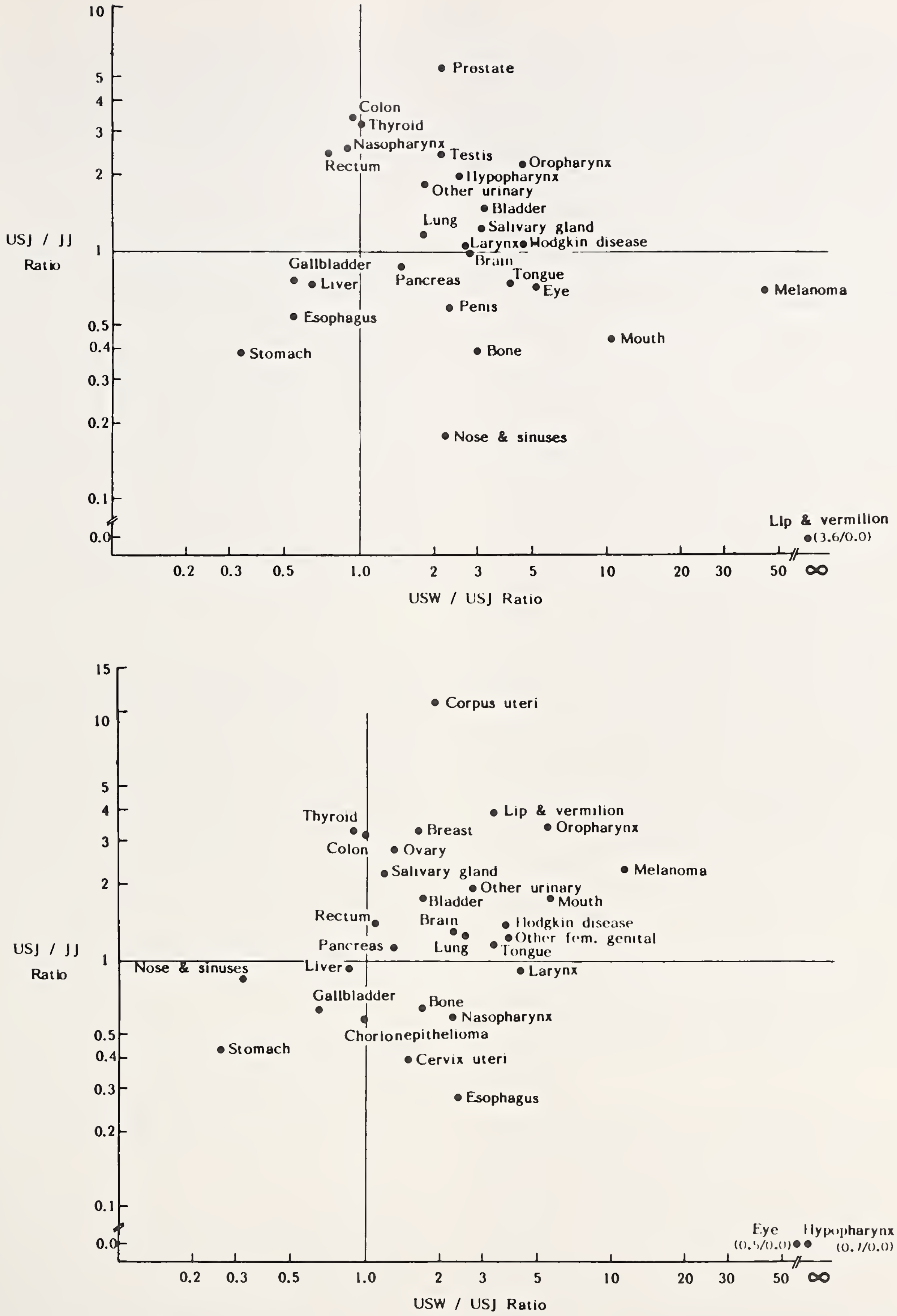


FIGURE 4.—Comparisons of the relative cancer incidence by site among JJ, USJ, and USW according to the USJ:JJ ratio and the USW:USJ ratio. *Top* = males; *bottom* = females.

demonstrated that dietary patterns were different between Hawaiians of Japanese ancestry and native Caucasians, and those differences could result in differences in the cancer incidence of selected sites such as the stomach, prostate, and breast. They also demonstrated that the dietary patterns of Nisei were different (more Americanized) from those of Issei or Kibei (born in Hawaii but traveled to Japan for 5 or more yr of childhood education). Thus further observations of differences in life-style, especially eating habits, and cancer incidence among USJ compared with those of JJ and USW would be a useful study of the relative importance of environmental and genetic factors in the etiology of cancer.

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Cancer Incidence Among Filipinos in Hawaii and the Philippines [1, 2]

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ABSTRACT—Cancer incidence rates were compared for Filipinos in Hawaii (1978–81) and Manila (1977). Data for Hawaii were from the statewide Hawaii Tumor Registry; those for Manila were from the Central Tumor Registry of the Philippines. In addition, time trends (4-yr intervals) for cancer among Filipinos in Hawaii were examined for the period 1962–81 and compared with corresponding patterns among Caucasians. For most cancer sites, the rates among Filipinos in Hawaii showed expected increases or decreases from the Manila rates. Notable findings included a dramatic increase in thyroid cancer rates among Filipino women in Hawaii (highest of all ethnic groups), a surprising lack of increase in female breast cancer rates in Hawaii, and a lower than expected increase in colon cancer rates in Hawaii. The time trend analyses showed remarkably similar patterns in Filipinos and Caucasians in Hawaii and no suggestion that differences between the 2 populations are decreasing over time. These observations indicate that useful clues to cancer etiology can be found by further study of the Filipino experience in Hawaii.—Natl Cancer Inst Monogr 69: 93–98, 1985.

Filipinos are currently one of the major migrant groups to the U.S. and constitute the largest single group of immigrants to Hawaii (*1*). Most Filipino migration to Hawaii occurred during the twentieth century; major migration began with males who came as plantation workers after 1910, whereas that of females is a more recent phenomenon, largely post-World War II (*2*). The estimated Filipino population for 1980 in Hawaii was approximately 104,000 (*3*). Males exceed females, yielding a sex ratio of 1.1 to 1. The age distribution of the 2 sexes also differs, with 12.2% of the males over 65 and 71.1% under 45, compared with only 5.1% of the females over 65 and 80.4% under 45. In view of the valuable insights into the etiology of cancer that have come from the study of other migrant groups to the U.S., especially the Japanese in Hawaii (*4–7*), an analysis of the cancer patterns for this recent immigrant group should also be rewarding.

In this paper, we examine the incidence of cancer among Filipinos in the Philippines and Hawaii and to a more limited extent in the San Francisco area of California. We also examine some recent time trends for cancer among this ethnic group in Hawaii in relation to the corresponding trends among Caucasians.

MATERIALS AND METHODS

Data resources for comparisons of cancer incidence among Filipino populations were limited. For the Philippines, incidence data were available for the Greater Metropolitan Manila area for the year 1977. These data were collected by the Central Tumor Registry of the Philippines, which recorded information on all cancer cases diagnosed in 24 leading hospitals in the greater Manila area during this period; denominator data were based on census information (*8*). These sources, used in computations of age-adjusted incidence rates by site, were reported at the previous conference in this series (*9*).

For Hawaii, incidence data on cancer have been collected by the population-based Hawaii Tumor Registry since 1960. For the period since 1973, this Registry has been part of the SEER Program of the National Cancer Institute. All cancer cases that occur in the State, with the exception of basal and squamous cell carcinomas of the skin, are recorded by this Registry. Ethnic identification is taken from the medical record and thus represents self-declared race. Denominator data for the period before 1970 were based on Census Bureau estimates for Hawaii. For the period since 1970, the age-, sex-, ethnic-specific population estimates were based on a combination of the latter source and data obtained in an annual household survey by the Health Surveillance Program of the Hawaii Department of Health (*10*). Age-specific and age-adjusted [World Population Standard (*11*)] incidence rates were computed for 5 quadrennia (beginning with 1962–66, ending with 1978–81) for the Filipino and Caucasian ethnic groups.

Data on Filipinos for the western U.S. were more limited than for Hawaii. The registry for the San Francisco Bay area, also a member of the SEER Program, provided numerator data on Filipinos for the population covered by the registry. However, no census data from which we could compute incidence rates were available.

RESULTS

Our original intent was to compare cancer incidence rates of Filipinos in 3 areas: the Philippines, Hawaii, and California. However, because denominator data were not available for the San Francisco region, we examined the proportional distribution of the various cancer sites among Filipinos in the San Francisco Registry and compared these results with those from the Hawaii Tumor Registry (table 1). As seen in the table, these distributions are remarkably similar. The most notable differences in men between the 2 areas are for lung cancer (which comprised 21% of all cancers in male Filipinos in San Francisco but only 14% in Hawaii) and colorectal cancer (which ac-

ABBREVIATION: SEER = Surveillance, Epidemiology, and End Results (Program).

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counted for 13% of all cancers in San Francisco but nearly 21% in Hawaii). In women, the most notable difference was for cervical cancer, which comprised 5% of the cancers in San Francisco but a much higher 13% in Hawaii. If we could assume that the overall Filipino incidence of cancer was the same in Hawaii and San Francisco, these findings would suggest that any comparison between Hawaii and the Philippines could be generalized to the rest of the western U.S. However, such an assumption may not be warranted, inasmuch as a comparison of total cancer incidence between San Francisco and Hawaii for other ethnic groups shows substantial differences (*12*). For example, the overall Japanese male cancer rate is 48% higher in Hawaii than San Francisco, the Chinese male rate is 24% higher in San Francisco, and the white female rate is 6% higher in San Francisco.

Table 2 shows the Filipino age-adjusted incidence rates for several major cancer sites in Hawaii and Manila. For the gastrointestinal sites, the shifts between the Philippines and the U.S. show the same patterns for men and women: increases for esophageal, pancreatic, colon, and rectal cancers; decreases for gastric and liver cancers. Of the sites showing increasing risks on migration, colon and rectal cancers are most striking. Of the sites showing decreasing risks, liver cancer is most striking. For the respiratory and urinary tract sites, the patterns also vary. Laryngeal cancer, lung cancer in males, and renal cancer show little change between Manila and Hawaii, whereas lung cancer in women and bladder cancer show notable increases. Thyroid cancer shows a threefold increase from Manila to Hawaii, with a constant sex ratio of about 3:1 in each location. Of the sex-related sites, prostate and corpus uteri cancers show substantial increases in Hawaii over Manila, breast and ovarian cancers show only slight increases, and cervical cancer shows a twofold decrease.

Because the Hawaii Tumor Registry had been collecting uniform data on cancer for ethnic groups in Hawaii since 1960, we were able to examine time trends in incidence among Filipinos. Tables 3 and 4 provide the average annual age-adjusted incidence rates for selected sites for each of 5 quadrennia. Fewer sites are shown for females than males because the small numbers of cases made the rates for the other sites unstable. The salient findings can be summarized as follows:

TABLE 1.—*Proportional distribution (%) of cancer by site among 2 Filipino populations in the U.S., 1978–80*

Cancer site	Males		Females	
	Hawaii	San Francisco	Hawaii	San Francisco
Esophagus	2.4	1.2	0.7	1.1
Stomach	3.6	3.3	3.7	1.1
Colon	11.4	9.3	5.9	6.5
Rectum	9.2	3.7	1.8	3.8
Liver	1.4	5.7	1.1	0.5
Pancreas	3.4	5.7	1.5	1.1
Larynx	1.4	0.8	0.0	0.0
Lung	14.2	20.7	7.3	9.7
Prostate	21.6	22.8	—	—
Bladder	3.4	0.0	1.8	0.0
Kidney	1.8	1.6	0.4	0.5
Thyroid	3.0	3.3	10.3	10.8
Breast	—	—	22.0	26.9
Cervix	—	—	12.8	4.8
Corpus	—	—	6.2	5.4
Other	23.2	27.6	24.5	27.8
All sites	100.0	100.0	100.0	100.0

TABLE 2.—*Age-adjusted cancer incidence among Filipinos living in Manila and Hawaii*[a]

Cancer site	Males		Females	
	Manila 1977	Hawaii 1978–81	Manila 1977	Hawaii 1978–81
Esophagus	3	5	1	2
Stomach	10	7	6	5
Colon	5	19	4	12
Rectum	6	16	4	5
Liver	20	4	6	2
Pancreas	3	5	2	3
Larynx	4	3	1	0
Lung	29	27	9	16
Bladder	3	6	1	6
Kidney	3	4	1	1
Thyroid	2	6	5	17
Prostate	8	33	—	—
Breast	—	—	31	36
Cervix	—	—	16	8
Corpus	—	—	2	14
Ovary	—	—	7	9

[a] Incidence rates are per 100,000 and are age-adjusted to the World Population Standard (*11*).

1) Gastrointestinal: Colon, rectal, and pancreatic incidence rates rise slightly but progressively among males; this pattern is not evident for colon cancer among females, however.

2) Respiratory: Lung cancer rates increase clearly and progressively in men but not women.

3) Urinary tract: Bladder cancer rates show an apparent increase over time in men but renal cancer does not.

4) Sex-related: Breast cancer rates rise progressively, with the greatest change in the most recent period, a pattern similar to that for prostate cancer which also shows a dramatic increase in recent years; corpus uteri rates increase slightly over time; and those for cervical cancer decline progressively and substantially.

5) Other: Thyroid cancer rates show no clear progression in either men or women; leukemias and lymphomas as a group have no clear pattern, though a decline is apparent for men in recent years.

For selected sites for which the rates were based on sufficient numbers of cases to yield some stability, we compared the Filipino trends with those for Caucasians in Hawaii over the same period (fig. 1). The trend for breast cancer in women of both ethnic groups is one of a general increase between 1962–65 and 1978–81. For prostate cancer, both groups also show increasing rates, but only for the most recent 2 intervals. Lung cancer rates reveal a

TABLE 3.—*Trends in cancer incidence among Filipino males in Hawaii, 1962-81*[a]

Cancer site or type	Intervals				
	1962-65	1966-69	1970-73	1974-77	1978-81
Mouth/pharynx	4.3	6.6	5.1	5.6	4.2
Esophagus	3.0[b]	2.6	5.4	6.5	4.8
Stomach	7.1	6.3	6.9	9.7	6.6
Colon	14.3	13.5	16.9	17.1	18.8
Rectum	12.4	12.5	13.3	14.9	16.2
Liver	7.5	9.6	4.9	9.9	4.1
Pancreas	2.4	4.9	5.7	6.6	5.3
Lung	15.9	20.2	20.6	26.3	27.3
Leukemias/lymphomas	11.0	12.4	12.0	10.6	6.9
Prostate	14.0	14.6	9.9	28.0	33.4
Bladder	2.7[b]	3.3[b]	3.9	6.6	5.7
Kidney	4.1	1.7[b]	3.8	4.5	3.7
Thyroid	5.0	3.8[b]	2.8	5.7	5.6

[a] Incidence rates are per 100,000 and are age-adjusted to the World Population Standard (*11*).

[b] Rate is based on fewer than 10 cases.

clear progression in both groups, but the rate of increase is greater in Caucasians (11.4% from 1974-77 to 1978-81 in Caucasians vs. 3.8% in Filipinos). An overall increase is seen for colon cancer for both groups during the interval; again, the rate of increase is greater in Caucasians (22.6% from 1974-77 to 1978-81 in Caucasian men vs. 9.5% in Filipinos). In general, these trends indicate that: 1) The secular trends in cancer incidence are similar for Filipinos and Caucasians in Hawaii; and 2) the differentials between Caucasian and Filipino rates are apparently not diminishing over time.

DISCUSSION

The limitations of the data used for this report must be apparent. The registration data for Manila assume that all resident cancer cases within the catchment area have been identified. This is unlikely because all cancers are probably not diagnosed nor are all patients seen in the hospitals covered by the registry. This underascertainment would lead to underestimation of the true incidence rates. On the other hand, the census data may underrepresent the actual numbers of residents in the catchment area, which would tend toward overestimation of the rates. The inclusion of any patients whose true residence was outside the greater Manila area would again lead to overestimation of the rates. Finally, not all residents of Manila are Filipino. Chinese, the largest non-Filipino group, constitute about 16% of the metropolitan population (*8*). To the extent that the cancer rates differ in Chinese, they will have some impact on the overall rates, which are taken to reflect Filipinos only. [Basa et al. (*8*) reported that nasopharyngeal and liver cancer rates in Manila were similar in Filipino and Chinese men but higher in Filipino than Chinese women; on the other hand, Chinese women had higher rates of breast and stomach cancers than did Filipino women.] It is not clear to what extent these sorts of errors might have affected the incidence rates reported here.

The quality of the numerator data for Hawaii and San Francisco is high. Both registries are population based and maintain high standards for ascertainment of cases, accuracy of recording diagnoses, and other aspects of quality control as part of the SEER Program. Furthermore, classification and coding between the 2 registries are uniform.

Because the comparison of the results for Manila with those in Hawaii was intended to illuminate the effects of migration, one should note whether the Manila popula-

TABLE 4.—*Trends in cancer incidence among Filipino females in Hawaii, 1962-81*[a]

Cancer site or type	Intervals				
	1962-65	1966-69	1970-73	1974-77	1978-81
Colon	6.4[b]	11.1[b]	14.8	10.1	11.6
Lung	17.3[b]	20.4	18.2	17.3	16.3
Leukemias/lymphomas	5.1[b]	7.6[b]	10.6	12.5	5.7
Thyroid	22.4	15.7	9.9	18.8	17.4
Breast	18.2	22.6	22.6	25.6	36.2
Cervix	16.6[b]	10.6[b]	14.2	7.0	7.5
Corpus	12.9[b]	12.8	15.9	14.1	14.1

[a] Incidence rates are per 100,000 and are age-adjusted to the World Population Standard (*11*).

[b] Rate is based on fewer than 10 cases.

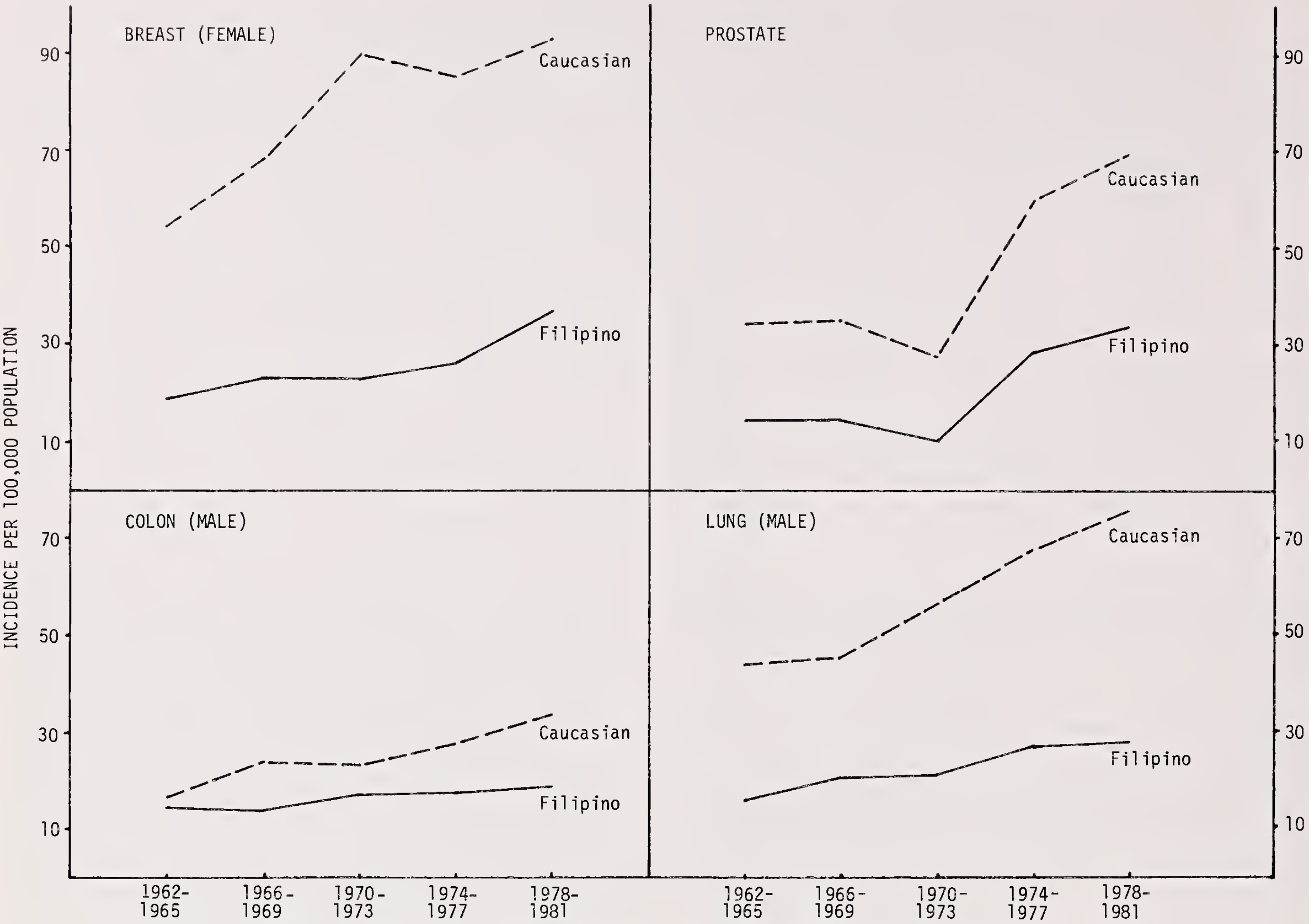

FIGURE 1.—Secular trends in cancer incidence among Filipinos and Caucasians in Hawaii.

tion's rates are representative of the home rates of the migrating group. Historically, the Filipino migrants to Hawaii have included proportionately more persons from the rural areas of northern Luzon and the Central Visayas Region (*2*). Thus the Manila Registry rates may not be entirely representative of the migrant group's home country rates. However, to the extent that the Manila rates differ, they would be expected to resemble more those of Filipinos in Hawaii and to reduce the extent of any differences observed between the 2 countries. Generally, however, the differences in the relative incidence of cancer by site in the urban and rural populations of Southeast Asia are not substantial (*13*). Furthermore, we had some data from another area of the Philippines, based on a partial survey of cancer incidence in Cebu in the Central Visayas Region (Alcantara AM, Villalon BG: Unpublished observations). The findings from the survey were similar to those from the Manila Registry with regard to the prominent sites of cancer. For example, of the 10 leading sites in Cebu, the overlap is almost complete with Manila, except for the greater prominence of cancer of the tongue in Cebu. [The latter cancer may be partially attributable to the chewing of betel nut, a practice more common in poorer rural areas than in larger cities like Manila (*8, 13*).] An additional piece of evidence on the relative lack of importance of intracountry variations on intercountry comparisons is the result of an analysis of cancer mortality data on Japanese in Japan and Hawaii. In this study, it was shown that the use of the more precise data from the specific prefectures of origin of the Hawaii migrants for the intercountry comparison had little effect on the observed cancer relationships (*14*).

The results of the comparison between Manila and Hawaii agree with the general observation that cancer risks in migrants show a progressive shift from the rates in the parent country to those in the host country (*4–7*). Thus increases are substantial between Manila and Hawaii in the incidence rates for colon, rectum, lung (in women), prostate, bladder, and corpus uteri cancers, all of which have relatively high rates in the U.S. compared with less developed or westernized countries like the Philippines (*11*). However, some exceptions occur. For example, the rate of lung cancer in men in Hawaii is not higher than that in Manila. Equally dramatic are the decreases from Manila to Hawaii in the risk for sites with lower rates in the U.S. generally, such as liver, cervix, and stomach.

A particularly notable finding was the substantial increase in risk for thyroid cancer in Filipino migrants to

Hawaii; reasons for this increase are not apparent. In general, thyroid cancer rates are not notably higher in the white populations of Western countries (*11*). Furthermore, the rates in Manila are already relatively high, as noted earlier, and thyroid cancer is one of the major cancer sites in both Manila and Cebu [(*8*); Alcantara A-M, Villalon BG: Unpublished observations]. Comparable data on Japanese migrants to Hawaii also show a similar degree of increase in both sexes (*7*), and the thyroid cancer rates in Hawaii among all ethnic groups are high in worldwide comparisons (*11*). Thus the increase among Filipinos may reflect a general increase in exposure to causal factors in Hawaii. Nevertheless, the rates of Filipino females are substantially higher than those of the other ethnic groups in Hawaii. The thyroid is one of the few cancer sites for which the Filipinos have the highest rates in Hawaii. The possibility that certain dietary exposures, including rich sources of iodide, are implicated etiologically will be explored in a case-control study currently in progress in Hawaii.

Another unusual finding among Filipinos is the failure of the colon cancer rates in the Hawaii migrants to rise to the same high rates seen in Caucasians. For example, among the Japanese, even the first-generation migrants showed an abrupt increase in incidence for this site to the same high level as that of the Caucasian population (*7*). On the basis of mortality data, Staszewski and Haenszel (*5*) made a similar observation on Polish migrants to the U.S. If the 2-stage theory of carcinogenesis is accepted, one could reasonably interpret the Japanese and the Polish experience to indicate that native Poles and Japanese are exposed to initiators of colon cancer to the same extent as Americans, whereas exposure to promotors is much greater in the U.S. This explanation would account for the substantial increase in incidence even among first-generation migrants who, primarily as adults, increase their exposure to the putative promotor, presumably dietary. On this basis, one might conclude that Filipinos are less exposed to the initiator(s) in the Philippines, so that an increased exposure to promotors in Hawaii does not result in the same high incidence as seen in Caucasians. Alternatively, the exposure to promotors among the Filipinos in Hawaii could be less than in Caucasians. The latter premise seems less likely, inasmuch as Japanese in Hawaii also maintain many of their traditional dietary patterns, and, e.g., have an average fat intake only slightly higher than Filipinos in Hawaii, yet their colon cancer incidence is almost four times as high as that of the Filipinos.

The incidence pattern for breast cancer between Manila and Hawaii is also unexpected. Breast cancer incidence in Manila is relatively low compared with that in our white population, yet it is high in comparison with the rest of Southeast Asia (*13*). Reasons for this higher risk are not known, although Basa et al. (*8*) found that breast cancer occurred more frequently in more highly educated women in Manila; this association is a consistent finding in Western populations as well (*15*). Whether other known risk factors for breast cancer, such as age at first full-term birth, can fully account for the higher breast cancer rates in Manila than the rest of Southeast Asia has not been established. Even more surprising is the failure of the incidence rates to increase among the Filipino migrants in Hawaii. Breast cancer rates among migrants to the U.S. are generally intermediate between the lower rates in the country-of-origin and the extremely high rates for white Americans (*4, 5, 16, 17*). Although we found this true for Japanese migrants to Hawaii (*7*), we do not see it in the Filipino data here.

The findings of the trend analysis and the comparison with Caucasian rates in Hawaii are also intriguing. Generally, most sites examined showed either progressive or no change over time, but for some sites the most notable changes occurred only in recent years (e.g., breast, prostate). In the comparison with Caucasians (fig. 1), the parallels in the trends are striking, which suggests that common environmental factors are influencing both the Filipino and Caucasian rates. However, the curves seem to

TABLE 5.—*Comparison of Filipinos and Caucasians in Hawaii on selected characteristics related to cancer risk*[a]

Exposure factor	Males		Females	
	Filipino	Caucasian	Filipino	Caucasian
Food consumption				
Coffee, cups/day	1.2	2.5	1.1	2.0
Pork, times/wk	2.1	0.8	2.1	0.6
Salted fish, times/wk	1.6	0.1	1.6	0.1
Rice, times/wk	11.4	3.5	10.7	3.0
Alcohol use				
Beer, % consuming >6 cans/wk	16.8	23.4	1.2	4.1
Spirits, % consuming >9 oz/wk	2.4	10.5	0.5	7.8
Cigarette smoking				
Ever smoked, %	52.4	60.5	26.0	46.5
Lifetime use among smokers, pack-yr	14.2	23.1	9.6	18.4
Anthropometry				
Height, in	65.1	69.7	61.0	64.3
Weight, lb	144.1	168.1	119.0	132.6
Education, No. of yr	10.2	13.1	10.0	12.7

[a] All data are mean values age-adjusted to the World Population Standard (*11*).

be running in parallel, which is not characteristic for migrant populations. Cancer rates in migrants generally increase (or decrease) at a greater rate than that of the indigenous population, so that the two come closer together with successive generations (*7, 17*). Why this does not seem to be occurring with the Filipinos is at present unclear. It is possible that the period examined is too brief for such cross-sectional data to reflect the impact of successive generations. Another possibility is that because of their relatively large numbers in Hawaii, Filipinos are better able to retain desired cultural behaviors, such as dietary practices, that have a beneficial effect on their cancer risks. Data from population surveys in Hawaii do show persistent differences between Caucasians and Filipinos in a number of characteristics, as shown in table 5. For example, Filipinos consume more rice and dried/salted fish than do Caucasians in Hawaii, but they smoke and drink alcohol to a lesser extent than do Caucasians. In addition, Filipinos have the lowest fat consumption of the 5 main ethnic groups in Hawaii (*18*). Filipinos are currently at a lower socioeconomic level than all other ethnic groups, except Hawaiians, and a large proportion work in active outdoor occupations, such as agriculture (*19*). Such occupations provide greater physical activity than do the usual types of employment of the Caucasian population.

In summary, Filipinos generally show the expected differences in incidence of cancer between their native country and Hawaii. The major exceptions are the substantial increase in thyroid cancer incidence in Hawaii, especially among women, the similarity in breast cancer incidence in the two settings, and the persistent low rate of colon cancer relative to Caucasians in Hawaii. In addition, secular trends in Hawaii do not indicate that Filipino–Caucasian differences are diminishing over time as has been observed in the Japanese population. These unusual findings suggest that clues to cancer etiology can be found by a more thorough study of the Filipino experience in Hawaii.

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Cancer in Hispanics in Los Angeles County [1, 2]

Thomas M. Mack, Ann Walker, Wendy Mack, *and* Leslie Bernstein [3]

ABSTRACT—Using ethnicity of surname, nativity, residential social class, and inferred age at migration to characterize and subdivide Hispanics in Los Angeles, we compared risk ratios and proportional incidence ratios to examine the patterns of occurrence of selected neoplasms within the Hispanic community. Common neoplasms for which Hispanics have high, low, and intermediary risk were examined in detail. Although the patterns expected on the basis of current concepts of etiology were generally found and served to reinforce presumptions about the biologic significance of the risk factors, a number of observations cannot be explained easily with current knowledge. The risks for stomach and bowel cancers do not conform to the mirror-image patterns to be expected on the basis of inverse patterns of dietary acculturation. Incidence of cancer of the breast, in contrast to that of cervix, does not appear to reflect early cultural practice. Consistent details in the patterns of cancers of the bladder, rectum, ovary, prostate, and possibly pancreas imply unrecognized determinants of disease. Gallbladder cancer in Hispanic women is the disease most closely tied to Hispanic origin or culture, or both, but the ethnic pattern in women differs greatly from that in men.—Natl Cancer Inst Monogr 69: 99–104, 1985.

Examination of the pattern of cancer occurrence by nativity, ethnicity, and residence sometimes provides clues to specific etiology. The Cancer Surveillance Program covers Los Angeles County, which contains the largest population of Hispanics in the U.S. and the largest population of Mexican or Central American origin covered by a population-based cancer registry. Nearly 10 years have passed since the pattern of cancer in Los Angeles Hispanics was described (*1*), and we are pleased to update that description in more detail.

MATERIALS AND METHODS

The University of Southern California Cancer Surveillance Program identifies each Los Angeles County resident in whom cancer is microscopically verified or for whom cancer is recorded on a death certificate (*2*). Using the hospital pathology report and medical record, Program personnel classify tumors by anatomic site and histologic morphology. Of the approximately 27,500 annual reports of cancer in white residents during the period 1972 through 1981, approximately 2,000 bear surnames of Spanish origin or have been born in a Spanish-speaking country, or both. Each case identified by the Registry is routinely characterized not only by race, birthplace, and ethnicity of surname (with the use of an augmented modification of the 1970 census list of Spanish surnames), but by sex, date of birth, residential address, and SSN (*3*). Registry staff use the residential address to characterize each case by an SES classification, which is based on the aggregation of 1970 census tracts in the County into quintiles according to both median income of tract families and the mean years of education of the heads of households residing in the tract.

Immigrants are classified by SSN and by approximate age at immigration to the U.S. in the following way: Digits 4 and 5 of the SSN have been assigned by the Social Security Administration in a particular sequence within each block of initial digits (*4*). Because most persons acquire their SSN when entering the work force or before, and most have already entered the work force by about the end of the second decade of life, the sequence of digits 4 and 5 is correlated with year of entering the work force and therefore with year of birth for U.S. natives. Assuming that most immigrants of known age receive their SSN assignment at the time of immigration, one can classify those born abroad on the basis of "early" migration in childhood (received numbers within the same sequence as natives of the same age) or "late" migration during adulthood (received numbers in a later sequence). Accordingly, immigrant patients with known birth dates and SSN were dichotomized by approximate age at immigration according to whether digits 4 and 5 in their SSN fell before (early) or after (late) the 90th percentile of digits in sequence held by 1980 California decedents born in California in the same 5-year period as the patient (50,391 natives are listed on the 1980 state mortality file).

Risks for subgroups of Hispanics were computed by 2 methods. Firstly, annual incidence rates were directly computed by the best available method. Hispanics were not identified by the 1980 census except by self-identification, and, for this reason, age- and sex-specific denominators for SSW and NSSW from the 1970 census were adjusted for undercounting (*5*), then adjusted for intercensus change (*6*). With nativity data from the 1970 census 2% public use sample, each Spanish-surnamed subgroup was subdivided into groups born in the U.S., Mexico, and elsewhere (*3*). For each of 16 anatomic site–morphology combinations chosen on the basis of frequency and early interest, TAAIR age-adjusted to the Standard World

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ABBREVIATIONS: SSN=Social Security number(s); SES=socioeconomic class; SSW=Spanish-surnamed whites; NSSW=non-Spanish-surnamed whites; TAAIR=truncated (≥35 yr) sex-specific, average annual incidence rate(s); PIR=proportional incidence ratio(s).

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Population (*7*) for the combined decade of study were prepared for NSSW, low SES (class 4–5) NSSW, total SSW, and Mexico-born SSW. The age groups under 35 years were excluded because of greater inaccuracy in census data for these ages among Hispanics. We then computed risk ratios using those rates. To provide outside reference standards from Hispanic countries, we prepared analogous annual TAAIR (≥30-yr age-adjustment was used because data were unavailable for mid-decade subdivisions) for each neoplasm with incidence and population data provided for the same decade for Cali, Colombia (courtesy of Dr. Carlos Cuello) and Lima, Peru (courtesy of Dr. Laura Olivares).

Because the population of Hispanics by age at immigration is unknown and the intercensus trends in immigration by specific age, national origin, social class, and surname category are matters for speculation, we did not attempt comparisons between subcategories of Hispanics using directly computed incidence rates. Instead, for each neoplasm, a second method was used. We computed an age-standardized PIR for each demographic subset, dividing the observed number of cases by an expected number derived from the total number of cancer cases in that subset (known nativity, age at immigration, social class, surname category). To get the expected number for each age-specific Hispanic subset, we multiplied this total number by the proportion of that cancer among all NSSW cancer patients of that age; these age-specific expected numbers were then summed. In general, we have found PIR by Hispanic subcategory to correspond well to directly computed risk ratios using standard assumptions about the trends in migration, and we conservatively prefer to use them when doubts exist about the accuracy of census-derived population estimates.

We used a likelihood ratio test (chi-square with 1 degree of freedom) to compute confidence limits around the risk ratio or PIR for each Hispanic subgroup compared with Los Angeles NSSW. Confidence limits were also used for 2 other comparisons, each made within groups of Mexico-born: non-Spanish-surnamed versus Spanish-surnamed patients and patients with early versus late age at migration.

RESULTS

In table 1 we present TAAIR for Los Angeles Hispanics, non-Hispanics, and low SES (4–5) non-Hispanics, and 2 sets of risk ratios based on the alternative assumptions that 1) the total non-Hispanic rate or 2) the low SES non-Hispanic rate offers the most appropriate standard of comparison. Generally, use of the low SES standard tends to minimize the difference between the Hispanic and non-Hispanic rates, but never by much; even for cervix cancer the adjustment was modest. Rates for cancers of the pancreas and prostate were closer to the overall non-Hispanic rate than to that for non-Hispanics of low SES. As previously observed, the most dramatic high-risk type is that for cancer of the gallbladder in females; other cancers for which Hispanics are at high risk are gallbladder in males, and cancers of the liver, cervix, and stomach. Pancreas and prostate cancers appear slightly more frequent in Hispanics, whereas others in the lower gastrointestinal tract, urinary tract, reproductive system, and respiratory system tend to be less frequent than among non-Hispanic persons. Melanoma occurs much less often among Hispanics than among other whites in Los Angeles.

Figure 1 provides a detailed comparison between subgroups of Hispanics for each neoplasm. In the first section, risk ratios for Spanish-surnamed natives of Mexico living in Los Angeles are compared with those for residents of Cali and Lima; again the Los Angeles NSSW are used as a standard of comparison. In the second section PIR are shown, with the same standard, for U.S.-born Hispanics overall and by SES, for Mexican immigrants by surname and age at migration, and for other Hispanic immigrant groups, i.e., those from the Caribbean (generally non-mestizo Cubans and Puerto Ricans); Central America (Salvadoreans, Guatemalans, and others); and South America (Ecuadorians, Colombians, Peruvians, and others). Note that comparisons within the first and second parts of the figure must be made cautiously because of the unavoidable difference in the basis for age adjustment. The figures are based on the following number of cases for all sites combined: 139,466 in Los Angeles NSSW; 3,254 in Spanish-surnamed Mexicans; 771, 954, and 3,711 in U.S.-born Hispanics of SES 1–2, 3, and 4–5, respectively; 483 in non-Spanish-surnamed Mexicans, 1,526 in early Mexican migrants; 1,728 in late Mexican migrants; and 691, 324, and 225 in persons born in the Caribbean, Central America, and South America, respectively. No PIR is shown if either the expected or the observed number of cases was less than 5.

Generally, Los Angeles Mexicans experienced a risk which was intermediate between that for their non-Spanish neighbors and that for residents of Cali and Lima, but there were exceptions. For cervix cancer, the 3 Hispanic groups seemed to experience about the same risk. Compared with rates in Cali and Lima, Mexicans in Los Angeles experienced even lower rates of melanoma and upper respiratory cancers and even higher rates of cancers of the liver and gallbladder (females).

Among immigrants to Los Angeles from various parts of Latin America, the most extreme risks fell to those born in countries of Central America other than Mexico; risks among females for cancers of the gallbladder and cervix were especially high, and among these immigrants, risks for colon and prostate cancers were unusually low.

It is apparent, when one looks at the PIR, that relatively affluent U.S.-born Hispanics had higher risks of prostate, breast, and endometrium cancers and of melanoma, and lower risks of cancers of the liver and cervix than the less affluent. They had an unexpectedly low risk of cancer of the ovary and pancreas.

For immigrants from Mexico, the risk gradient from Spanish-surnamed to non-Spanish-surnamed usually ran in parallel with the same gradient for U.S. natives. Although the non-Spanish-surnamed Mexican patients were sometimes small in number, the probability that chance could account for the observed differences between the 2 subcategories was less than .10 for stomach, rectum, and prostate cancers in men; for stomach and liver cancers in women (<.05); and for melanoma in men and women. The gradient from late to early age at immigration from

TABLE 1.—*The TAAIR (≥35 yr) for Los Angeles County residents by sex according to Spanish surname and SES for selected neoplasms*

Cancer site	Annual TAAIR/100,000						Risk ratio	
	NSSW total	No.	NSSW Low SES	No.	SSW	No.		
	(1)		(2)		(3)		(3)/(1)	(3)/(2)
Stomach								
Males	30.4	2,861	29.7	1,239	64.5	619	2.1	2.2
Females	14.8	2,108	14.4	934	30.6	387	2.1	2.1
Colon								
Males	93.3	8,661	79.8	3,328	63.3	618	0.7	0.8
Females	75.3	10,585	67.0	4,295	51.4	659	0.7	0.8
Rectum								
Males	44.1	4,177	39.5	1,651	38.2	391	0.9	1.0
Females	27.2	3,759	23.9	1,493	21.4	281	0.8	0.9
Liver								
Males	5.9	551	5.9	248	15.4	156	2.6	2.6
Females	2.5	339	2.6	156	7.0	86	2.8	2.7
Gallbladder								
Males	2.1	197	2.2	91	6.0	48	2.9	2.7
Females	3.3	481	3.4	227	16.8	214	5.1	4.9
Pancreas								
Males	25.8	2,435	22.3	935	29.0	286	1.1	1.3
Females	17.3	2,413	15.9	1,003	20.3	251	1.2	1.3
Oropharynx								
Males	43.9	4,362	45.9	1,916	30.0	329	0.7	0.7
Females	18.8	2,463	17.5	973	10.9	151	0.6	0.6
Larynx								
Males	21.4	2,116	21.7	907	16.9	187	0.8	0.8
Females	4.0	516	4.5	240	3.2	41	0.8	0.7
Lung								
Males	184.9	17,861	189.3	7,922	126.3	1,225	0.7	0.7
Females	70.5	9,204	67.2	3,726	47.7	630	0.7	0.7
Prostate	163.2	14,609	141.0	5,893	183.0	1,459	1.1	1.3
Breast[a]	223.4	28,837	177.8	9,693	160.3	2,471	0.7	0.9
Endometrium	86.3	11,085	66.2	3,602	51.2	769	0.6	0.8
Ovary	35.3	4,580	29.9	1,654	27.1	406	0.8	0.9
Cervix	19.5	2,443	23.7	1,176	54.2	920	2.8	2.3
Bladder								
Males	74.3	6,968	62.6	2,610	47.5	424	0.6	0.8
Females	19.4	2,700	16.2	1,029	13.0	164	0.7	0.7
Melanoma								
Males	26.5	2,735	18.5	756	7.2	89	0.3	0.4
Females	19.1	2,408	14.2	750	6.7	107	0.4	0.5

[a] Data are for female breast only.

Mexico ran in parallel with that from Spanish to non-Spanish surname for most sites, and statistical significance at the .05 level was reached for colon, rectum, and bladder cancers in men, and gallbladder, breast, cervical, and oral cancers in women. The difference for liver cancer in men was also significant if the level were set at .10.

For some sites the age-at-migration gradients did not run parallel to those based on surname; for cancers of the stomach (and possibly for melanoma and prostate cancer), they even ran counter to expectation. The pattern was always consistent for the 2 sexes, but chance could not be excluded as an explanation for any single sex-site difference even at a liberal .10 level.

DISCUSSION

Investigators have usually performed migrant studies to test a hypothesis of environmental cause against the alternative of racial or other inherited etiology (*8*). Unfortunately, things are rarely that simple because a person's decision to migrate may not always or even ever be independent of detailed racial or ethnic origins. The environmental exposures and medical practices of immigrants are usually different from those of natives because of personal choice and limitations of circumstance. Furthermore, immigrants have an increased propensity to return periodically for visits to the homeland.

Moreover, important distinctions must be made between categories of acquired risk, and these further complicate the interpretation of migrant studies. Just as an increase in risk to the siblings of an affected person may imply either a genetic component or, alternatively, a risk conveyed by some household exposure, so the persistence of a risk characteristic of the place of origin among migrants in a new setting may have several alternative explanations: inherited susceptibility, a similar extreme in SES, an early environmental exposure followed only after a long latency by manifest disease, or continued exposure to some element transported with the immigrant as part of the cultural "baggage." If the high risk is retained by those in subsequent generations who are life-long expatriates, only the second of the three explanations is ruled out.

Finally, as our understanding of the etiology of neoplasms increases, we come to realize that, whether or not an inherited element in etiology can be specified, the environmental determinants are inevitably multiple, and these co-factors often seem to act at different times in relation to the onset of the tumor. Therefore, in many instances exposure to various determinants may occur at different stages in the sequence of migration.

Accordingly, we attempted to combine available demographic markers to describe simultaneously each facet of the risk in connection with migration: place of residence, birthplace, SES, ethnic identity, and age at migration. Space will not permit a detailed review of the literature for each of the neoplasms we have chosen, and, as indicated above, chance sometimes offers a reasonable alternative to the biologic interpretation we offer. We have provided biologic interpretations for most observations because this is a hypothesis-generating, not a hypothesis-testing, exercise and such detailed observations rarely are used to shape hypotheses.

Of the neoplasms studied, melanoma is known to be much less common in those with a genetically determined dark skin (*9*), and even though it might be expected to occur slightly more often after cumulative exposure to the lower latitudes of Mexico, variations in risk of melanoma among Hispanic groups probably reflect largely genetic differences. If we assume this to be true, surname appears to provide a generally good predictor of racial skin color for both native and Mexican-born whites. In addition, high SES in Spanish-surnamed women tended to correlate with higher risk. This suggests a higher prevalence of mixed marriages among the affluent but does not totally exclude an alternative explanation. If the increased frequency of past solar exposure, which is presumably responsible for the strong correlation elsewhere between SES and risk in non-Hispanic whites of both sexes (*9*), is responsible for such a finding, it is not clear why it is true here only in Hispanic women. There was little correlation among Hispanics in Los Angeles between birthplace or age at migration and risk from melanoma, and no strong correlation between birthplace or age at migration and skin color.

Los Angeles residents born in Mexico and the Caribbean had rates of lung cancer lower than those of non-Hispanics, regardless of SES, surname, or age at migration. These rates were substantially higher than those for persons born in South America, whether now in Los Angeles or still in Cali or Lima. If this pattern reflects smoking practices, it suggests that they are an aspect of U.S. culture rapidly adopted by Hispanic immigrants, at least those from contiguous countries.

Bladder cancer showed a similar pattern of risk, but among U.S.-born Hispanic women risk was higher among those of high SES, just as it is in non-Hispanic women in Los Angeles (*10*). For cancer of the larynx and oral cavity, only those from Cali have higher risks than do Los Angeles Hispanics; otherwise, no consistent pattern of risk was evident.

Cervix cancer is as common in Mexicans in Los Angeles, including those currently possessing non-Spanish surnames, as it is in South America. The inverse association with SES is as strong in U.S. Hispanics as in non-Hispanics (*11*), and risk is much higher among those who grew up in Mexico than among those who emigrated as children. The latter observation increases confidence in the significance of the classification by age at migration, and the pattern in general suggests an environmental determinant which acts early in life. Either a venereal infection with a long latent period or early marriage to a potential vector for such an infection would fit such a description.

Risk for cancers of the breast and endometrium in Los Angeles Mexcians, regardless of surname, is nearly as low as in South America, and the expected direct association with SES is strong in U.S. Hispanics. Hispanics from the Caribbean in Los Angeles, in contrast to Cubans in Cuba (*9*), tended to have risks from both diseases which are comparable to those in non-Hispanics, and early migrants had only a slightly higher (breast) or even a lower (endometrium) risk than late migrants. This pattern is suggestive of environmental determinants which operate late rather than early in life and which reflect the surrounding cross-cultural milieu, rather than long-retained cultural practices. For example, they do not suggest a dietary legacy from childhood.

The pattern of ovarian cancer did not completely parallel that for the breast and endometrium. Among U.S.-born Hispanics, risk was inversely associated with SES, a trend which is not only opposite to that for breast and endometrium but opposite to the trend for ovarian cancer in non-Hispanic whites in Los Angeles (*12*). This trend would not be expected if poor Hispanics have higher parity and if higher parity is protective. We can suggest no obvious explanation.

Risk from prostate cancer generally reflected place of current residence, again with little effect from birthplace, surname, or age at migration. The SES effect was direct, as in non-Hispanics (*13*), and equally obscure in origin.

Perhaps the most interesting pattern seen was that for risk of stomach cancer, which is high for all Hispanics, including those born in the U.S., in Mexico with or without Spanish surnames, and (to the least degree) in the Caribbean. These observations are consistent with previous ones (*14, 15*). Because Hispanics from the Caribbean, South America, Central America, and Mexico vary greatly in the proportion of inheritance which is Amerindian, the most plausible explanation for this pattern of stomach cancer risk is on the basis of some strongly retained common aspect of Hispanic cultural practice, di-

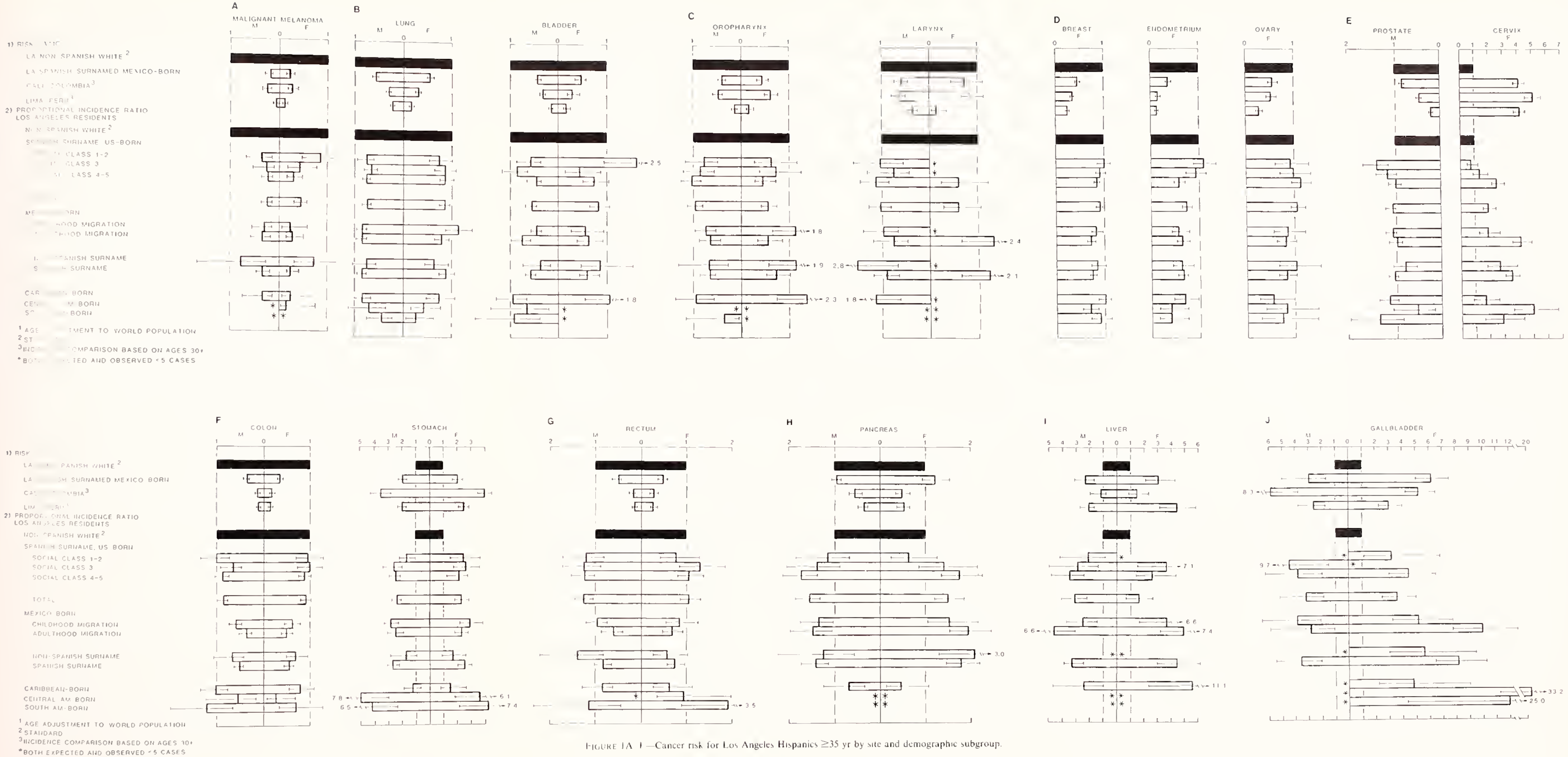

FIGURE IA-1—Cancer risk for Los Angeles Hispanics ≥35 yr by site and demographic subgroup.

etary or otherwise. No effect of SES was apparent among U.S.-born Hispanics, making it appear that the *quality* of life is less important to this disease than the chosen *style* of life. Most surprisingly, those who migrated late were not at higher risk but even seemed to be consistently at a slightly lower risk than those who migrated early. Other than attributing this finding to chance, we find it hard to offer an explanation for higher risk after early migration; it might represent a complex cohort effect, some other subtle change in the source of immigrants to the U.S., or, possibly, confounding by a dietary or other form of indigenous protection, which is less long-lasting than the effects of the cultural causation (*16*).

The pattern of colon cancer risk is in contrast to that of stomach cancer. Hispanics born in the U.S., regardless of SES, appear to lose the low-risk characteristic of Latin America and substitute the high risk experienced by their neighbors in Los Angeles; childhood migrants acquire this higher risk more completely than do those who migrate at an older age. This pattern resembles that of lung or breast cancer more than the inverse of stomach cancer. It constitutes additional evidence (*17*) that suggests determinants deriving from the modern U.S. economic milieu acting in adulthood rather than in childhood.

Risk from cancer of the rectum follows a similar pattern to that from cancer of the colon, except that U.S.-born Hispanics, non-Spanish surnamed Mexicans, and South American natives at present all appear to have a risk which is even higher than that of non-Hispanics. A similar "overshoot" has also been recognized in first-generation immigrants from the Orient (*18*) and may represent a mechanism which is similar to that postulated to produce higher risk of stomach cancer after early migration. The effects of an acquired environmental determinant may be more rapidly expressed than of an unknown resistance factor also acquired in Los Angeles, the latter could be either induced by the causal determinant, more gradually adopted by immigrants, or only expressed after a longer interval.

Pancreas cancer is more common in non-Hispanic Americans than in residents of Cali and Lima, but it is even more common in U.S. Hispanics, particularly those of lower SES and in those Mexicans who immigrated as adults. It seems to be less common in Hispanics of Caribbean origin than in non-Hispanics. No simple biologic explanation for this pattern can be offered, and it is certainly not consistent with an important role for dietary fat (*19*). Because pancreas cancer rates are notoriously sensitive to changes in medical practice and diagnostic convention, the pattern may reflect differences in medical care practice.

Liver cancer occurs more often in Mexicans than in residents of Cali. In Lima, Dr. Olivares indicates that metastatic cancers of the liver are not systematically excluded from the anatomic rubric, and the true rates are not as high as they appear. In Los Angeles, hepatoma occurs more often in late migrants and among men of lower SES. This pattern generally parallels that of cervical cancer and is similarly consistent with late expression of an early viral exposure (*20*).

Finally, the most extreme variations in risk among Hispanics are those for gallbladder cancer. Among women in Los Angeles, risk is higher in Mexicans (and is even more extreme in immigrants from Central and South America) than in residents of either Cali or Lima. However, this diagnosis is rarely based solely on clinical evidence because these rare tumors are not easily distinguished clinically from the more common liver and pancreas cancers. Because clinical diagnoses are more often necessary in developing countries, these international differences may be artificial. In Hispanic Americans, as in other white Americans (*21*), risk is associated with low SES, and in Mexicans it is associated with late migration and a Spanish surname. High risk has been observed in Chileans (*14*), who are genetically quite different from Mexicans. Among Hispanic men, who are at high but not extreme risk, the risk gradients for surname, age at migration, and even SES are inconsistent with those for women. This pattern supports the suggestion of an early cultural determinant, like that for cancer of the cervix or liver, but in this instance one which is greatly dependent on a sex-specific factor or factors. Dietary determinants of gallstones, greatly modified by reproductive factors, might produce effects consistent with such a pattern.

In summary, review of the pattern of occurrence of individual neoplasms in the Hispanic minority of Los Angeles continues to produce many presumably explicable but currently unexplained facts. Among those neoplasms for which Hispanics are at extreme high or low risk are some for which the source of the difference is probably genetic, such as melanoma, some for which it is probably behavioral, such as cervical cancer, and some for which the pertinent factors appear to be cultural, possibly dietary, but which currently remain a matter for speculation; this list would include cancers of the stomach and gallbladder. Other tumors, such as those of the colon, breast, and lung, appear less dependent on genetic or cultural heritage and seem to be more closely related to common factors and practices which cross genetic and cultural boundaries in the Los Angeles environment. We should address the obvious questions posed by the cancers which differ greatly in incidence between Hispanics and non-Hispanics, but we should also keep in mind that the undramatic patterns of certain tumors with respect to Hispanic origin also provide solid information that may be useful in evaluating causal hypotheses.

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Cancer Incidence in the Pacific Basin [1]

Herman R. Menck [2] *and* Brian E. Henderson [3]

Earlier reports have shown the diversity of cancer patterns among the populations within the Pacific Basin (*1, 2*). This report updates and adds to the previous information and re-summarizes some earlier data for comparison purposes. The data were classified by ethnic group and within ethnic group by geographic location (tables 1, 2). Ethnic groups covered include Japanese, Chinese, Korean, Filipino, Malay, Asian Indian, Polynesian, Melanesian, Latin American, Alaskan Native, and European. For all groups but the Malays and Indians of Singapore and the Koreans there are locations representing primarily native populations and locations representing migrant populations. The data were submitted by 17 registries (table 3).

It is not possible for us to assess the degree of completeness and correctness of each registry's report(s) nor the basic pattern of medical practice that the data inherently reflect. The operations of each of the registries have been described in detail at previous symposia (*3, 4*).

Contributors were asked to submit data classified to the primary site categories shown in table 2, using the topography and morphology sections of the International Classification of Diseases (*5*) or the closest approximation to that schema that their coding practices allowed. Incidence rates adjusted to the world population (*6*) of age groups 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70 and more years were calculated by the direct method.

ABBREVIATION: AAIR = age-adjusted incidence rate(s).

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TABLE 1.—*Average annual AAIR of all cancers combined in the Pacific Basin*

Ethnic group	Registry	Period	Male		Female	
			No.	Rate	No.	Rate
Japanese	Osaka	1978–80	24,683	220.9	19,386	137.1
	Hawaii	1978–80	1,235	229.2	1,048	182.1
	San Francisco	1973–77	159	180.0	266	212.0
	Los Angeles	1978–80	362	171.9	409	166.6
Chinese	Shanghai	1978–80	23,527	251.8	16,788	139.6
	Hong Kong	1978–80	17,605	276.4	13,609	189.6
	Singapore	1973–77	7,441	279.0	5,421	165.0
	Hawaii	1978–80	266	238.2	246	246.6
	San Francisco	1973–77	815	262.0	730	268.0
	Los Angeles	1978–80	261	187.8	229	151.3
Korean	Los Angeles	1978–80	90	174.6	116	126.3
Filipino	Manila	1977	1,258	136.0	1,409	131.0
	Hawaii	1978–80	499	182.6	277	187.6
	Los Angeles	1978–80	192	122.3	182	120.6
Malay	Singapore	1973–77	507	114.0	407	95.6
Indian	Singapore	1973–77	483	137.0	220	147.0
	Fiji	1980–82	108	53.7	271	124.5
Polynesian	New Zealand Maori	1978–80	619	351.5	680	336.8
	Hawaii	1978–80	498	345.9	501	279.4
Melanesian	Fiji	1980–82	201	81.5	329	118.4
	New Caledonia	1977–81	151	157.8	149	144.3
Latin American	Cali, Colombia	1978–80	1,657	219.8	2,243	218.7
	Lima, Peru	1978	1,629	121.9	2,288	147.8
	San Francisco	1978–80	721	201.1	827	179.8
	Los Angeles	1978–80	2,990	206.1	3,634	183.2
Alaska Native	Alaska	1978–82	277	274.2	254	230.3
Black	San Francisco	1978–80	2,032	391.7	1,640	258.8
	Los Angeles	1978–80	3,646	333.6	3,439	230.4
European	New Caledonia	1977–81	301	319.2	221	236.6
	New South Wales	1977–79	7,113	254.9	6,402	200.0
	New Zealand	1978–80	12,842	274.8	13,026	249.9
	Hawaii	1978–80	1,423	354.7	1,400	336.3
	British Columbia	1978–80	13,614	288.0	12,334	242.7
	Seattle	1978–80	12,791	301.8	12,615	255.7
	San Francisco	1978–80	13,971	338.9	15,300	288.9
	Los Angeles	1978–80	27,104	319.2	31,356	301.1

TABLE 2.—*Average annual AAIR of cancer by primary site in the Pacific Basin*

Ethnic group	Registry	Lip		Tongue		Salivary gland		Mouth		Naso-pharynx		Other pharynx		Esophagus	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F
Japanese	Osaka	0	0	1	0	0	0	1	0	1	0	1	0	8	2
	Hawaii	0	0	3	1	1	0	2	1	1	0	2	0	3	1
	San Francisco	0	1	1	1	1	4	0	1	0	0	1	0	7	1
	Los Angeles	0	0	0	0	1	0	2	0	0	0	2	1	2	1
Chinese	Shanghai	0	0	0	0	1	0	1	1	4	2	1	0	24	9
	Hong Kong	0	0	3	1	1	1	3	1	32	14	3	1	20	4
	Singapore	0	0	2	0	1	1	2	1	19	7	3	0	18	4
	Hawaii	0	0	3	0	1	2	1	1	10	5	1	0	2	0
	San Francisco	0	0	2	0	2	3	2	2	14	7	3	0	8	1
	Los Angeles	0	0	1	2	1	0	1	0	8	6	1	0	3	1
Korean	Los Angeles	0	0	0	0	3	0	0	0	0	2	0	0	2	0
Filipino	Manila	1	0	2	1	0	0	3	2	5	2	2	3	3	1
	Hawaii	0	0	3	0	0	1	3	5	3	2	1	1	4	1
	Los Angeles	0	0	2	0	1	0	0	1	3	1	1	1	0	0
Malay	Singapore	0	0	1	0	1	0	1	1	5	1	1	1	1	3
Indian	Singapore	0	0	4	0	1	0	8	8	1	0	4	4	7	8
	Fiji	0	0	2	2	0	1	1	0	1	0	0	0	1	3
Polynesian	New Zealand Maori	0	0	1	0	1	0	1	0	2	1	2	1	6	1
	Hawaii	0	0	1	1	1	2	2	3	1	0	3	1	11	1
Melanesian	Fiji	0	0	1	1	1	0	0	0	0	0	0	0	2	0
	New Caledonia	0	0	1	0	2	1	4	0	3	0	3	4	13	0
Latin American	Cali, Colombia	1	0	2	1	1	1	2	2	1	0	3	1	4	4
	Lima, Peru	0	0	0	1	1	1	1	0	0	0	1	0	2	1
	San Francisco	0	0	1	1	0	0	3	0	0	0	3	1	3	0
	Los Angeles	1	0	1	1	1	0	2	1	0	0	3	1	2	1
Alaska Native	Alaska	0	0	0	2	1	0	1	5	9	7	0	0	7	3
Black	San Francisco	1	0	4	1	1	1	4	2	1	0	6	2	12	4
	Los Angeles	1	0	4	1	1	1	4	2	1	0	6	2	12	4
European	New Caledonia	0	0	5	1	0	1	7	5	1	0	12	1	13	0
	New South Wales	5	1	2	1	1	1	3	1	1	0	3	1	4	2
	New Zealand	4	1	2	1	1	1	1	0	0	0	2	0	5	3
	Hawaii	2	0	4	2	1	0	6	5	1	0	5	4	3	1
	British Columbia	3	1	2	1	1	1	2	1	1	0	2	1	4	2
	Seattle	2	0	2	2	1	1	3	2	1	0	3	2	4	1
	San Francisco	3	0	4	2	1	1	4	3	1	0	5	2	4	2
	Los Angeles	4	1	3	2	1	1	4	3	1	0	4	2	4	1

TABLE 2.—*Average annual AAIR of cancer by primary site in the Pacific Basin (continued)*

Ethnic group	Registry	Stomach		Colon		Rectum		Liver		Gallbladder		Pancreas		Nasal sinus		Larynx		Lung	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Japanese	Osaka	75	36	10	7	9	6	27	7	4	4	7	4	1	1	4	1	35	10
	Hawaii	31	14	34	20	19	9	6	2	1	1	8	5	1	1	4	1	35	11
	San Francisco	24	24	26	25	18	5	3	1	2	1	6	6	0	1	3	0	29	7
	Los Angeles	28	11	24	20	14	10	1	2	0	1	5	9	0	0	1	0	33	7
Chinese	Shanghai	59	23	8	7	10	7	36	11	2	2	5	4	1	1	4	1	56	18
	Hong Kong	21	10	16	13	13	9	34	8	4	3	3	3	2	1	10	1	58	24
	Singapore	43	18	14	13	14	8	31	7	2	2	4	2	1	1	7	1	68	20
	Hawaii	11	13	31	24	13	8	9	3	1	0	8	8	0	0	3	0	41	23
	San Francisco	14	7	28	21	17	11	18	4	2	2	7	6	1	1	4	0	58	26
	Los Angeles	11	6	24	11	15	5	18	5	1	1	5	2	0	0	1	0	38	15
Korean	Los Angeles	41	14	7	5	3	10	7	5	7	7	15	3	2	1	3	1	32	14
Filipino	Manila	10	6	5	4	6	4	20	6	1	1	3	2	0	0	4	1	29	9
	Hawaii	6	7	20	12	18	4	3	2	1	3	6	3	1	0	3	0	28	14
	Los Angeles	5	3	14	4	6	6	4	1	3	2	4	2	3	0	1	0	17	5
Malay	Singapore	10	7	5	3	6	4	17	6	1	1	1	2	1	0	3	0	26	6
Indian	Singapore	19	10	8	5	7	4	13	4	1	3	2	4	1	1	5	0	17	6
	Fiji	4	5	3	3	2	1	0	0	2	4	1	2	0	0	3	0	2	1
Polynesian	New Zealand Maori	34	20	10	14	13	5	12	4	3	2	13	5	1	1	5	1	110	81
	Hawaii	40	18	25	11	17	8	7	3	1	1	9	8	1	0	6	3	95	29
Melanesian	Fiji	8	2	5	2	3	3	9	5	2	1	1	1	1	0	0	0	6	1
	New Caledonia	16	7	6	0	2	2	17	6	0	0	4	5	3	1	3	1	34	14
Latin American	Cali, Colombia	48	26	5	7	4	4	3	2	5	10	6	4	2	1	6	2	25	10
	Lima, Peru	27	16	5	5	3	3	6	5	2	5	4	4	1	1	3	0	18	6
	San Francisco	11	6	21	11	11	6	1	1	3	4	8	4	0	0	4	1	34	16
	Los Angeles	15	8	15	12	10	6	4	2	2	5	8	5	0	0	4	0	31	11
Alaska Native	Alaska	27	2	34	44	10	8	8	3	5	6	5	7	0	0	5	0	70	18
Black	San Francisco	20	7	29	30	13	9	6	2	2	2	15	8	1	0	10	2	104	29
	Los Angeles	15	7	26	23	12	9	5	1	1	1	10	7	1	1	6	2	78	25
European	New Caledonia	12	6	14	8	13	5	8	0	3	1	4	3	0	1	5	0	51	7
	New South Wales	13	6	22	20	14	9	1	0	2	2	8	4	1	0	5	1	51	10
	New Zealand	15	6	28	31	17	13	2	1	2	2	8	6	1	0	4	1	57	14
	Hawaii	10	6	33	26	16	7	4	2	1	2	9	9	1	1	9	2	63	33
	British Columbia	13	6	23	23	16	10	3	1	2	2	10	7	1	0	5	1	56	19
	Seattle	7	3	27	24	14	11	2	1	1	1	8	6	3	1	6	1	65	26
	San Francisco	12	5	34	25	18	11	3	1	2	2	10	7	1	0	7	1	72	32
	Los Angeles	10	5	31	26	16	11	2	1	2	2	8	6	1	0	7	2	64	30

TABLE 2.—*Average annual AAIR of cancer by primary site in the Pacific Basin (continued)*

Ethnic group	Registry	Breast		Cervix	Corpus	Ovary	Other female	Prostate	Testis	Other male	Kidney		Bladder		Melanoma	
		M	F	F	F	F	F	M	M	M	M	F	M	F	M	F
Japanese	Osaka	0	17	15	2	4	1	4	1	1	3	1	7	2	0	0
	Hawaii	0	50	12	17	1	0	31	1	0	8	2	8	7	2	0
	San Francisco	0	56	17	20	12	3	14	3	0	5	1	6	3	0	2
	Los Angeles	0	43	6	15	11	1	17	2	0	3	2	9	3	0	1
Chinese	Shanghai	0	13	9	2	4	2	2	1	1	2	1	7	2	0	0
	Hong Kong	0	29	26	6	6	2	6	1	1	3	2	16	5	1	1
	Singapore	0	22	18	4	6	1	4	1	1	3	2	7	2	1	0
	Hawaii	0	63	22	25	11	1	22	1	2	6	2	18	2	1	4
	San Francisco	0	60	31	20	12	4	18	2	1	4	2	11	2	0	1
	Los Angeles	0	36	9	9	5	1	10	1	0	5	2	8	2	3	1
Korean	Los Angeles	1	12	17	0	8	3	9	0	0	3	1	15	1	0	1
Filipino	Manila	1	31	16	2	7	7	8	1	1	3	1	3	1	2	2
	Hawaii	0	41	21	12	9	1	35	1	0	3	1	6	4	1	0
	Los Angeles	0	36	9	6	5	1	28	0	0	1	1	6	3	2	1
Malay	Singapore	0	15	9	4	10	1	6	1	1	1	1	3	0	1	0
Indian	Singapore	0	27	25	7	7	0	7	1	1	3	0	3	1	0	1
	Fiji	0	21	35	5	6	4	5	1	1	1	2	5	1	0	0
Polynesian	New Zealand Maori	2	61	42	16	12	2	37	8	2	7	3	4	6	2	1
	Hawaii	0	95	21	16	9	2	41	3	1	7	2	11	5	1	2
Melanesian	Fiji	1	20	34	5	12	2	5	1	0	1	2	0	1	2	1
	New Caledonia	0	17	32	9	4	7	4	1	1	1	0	5	6	0	0
Latin American	Cali, Colombia	0	36	44	6	9	5	35	1	3	3	2	10	3	3	3
	Lima, Peru	0	26	36	4	5	3	16	1	1	2	1	5	2	1	1
	San Francisco	0	50	13	12	7	2	36	2	1	8	2	11	3	2	4
	Los Angeles	0	44	18	14	8	3	42	3	2	7	4	10	3	3	3
Alaska Native	Alaska	0	44	31	2	7	2	30	3	0	6	6	7	2	1	0
Black	San Francisco	1	71	16	13	11	3	86	2	2	6	4	11	4	1	1
	Los Angeles	1	59	14	12	9	5	80	1	2	8	4	11	5	3	3
European	New Caledonia	0	43	18	12	8	6	24	6	0	1	1	8	1	10	4
	New South Wales	0	53	11	9	9	2	30	3	1	7	4	16	5	15	16
	New Zealand	1	60	24	11	11	2	36	6	1	8	3	14	3	15	21
	Hawaii	0	87	33	27	11	5	57	3	1	11	5	25	6	30	20
	British Columbia	1	69	12	17	11	2	53	3	1	9	4	14	4	6	8
	Seattle	0	71	8	24	11	3	61	4	0	8	4	19	5	7	7
	San Francisco	1	85	8	27	13	2	55	5	1	9	4	22	6	12	9
	Los Angeles	1	85	9	28	15	5	49	5	1	9	4	23	7	15	13

TABLE 2.—*Average annual AAIR of cancer by primary site in the Pacific Basin (continued)*

Ethnic group	Registry	Eye		Central nervous system		Thyroid		Bone		Connective tissue		Hodgkin's disease		Non-Hodgkin's lymphoma		Multiple myeloma		Leukemia	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Japanese	Osaka	0	0	3	3	2	3	1	1	1	1	0	0	9	2	1	1	5	3
	Hawaii	1	0	2	2	6	7	0	0	1	1	1	0	6	6	1	1	4	4
	San Francisco	0	0	4	4	2	8	0	0	3	0	0	0	9	1	2	0	4	3
	Los Angeles	0	0	6	2	3	6	0	0	1	0	0	0	4	3	2	2	4	3
Chinese	Shanghai	0	0	4	2	1	3	2	2	1	1	1	0	3	2	1	0	5	4
	Hong Kong	0	0	2	2	2	5	2	1	2	2	1	0	7	5	1	1	6	5
	Singapore	0	0	2	2	2	4	1	1	1	1	1	0	4	2	1	1	5	4
	Hawaii	0	0	5	1	10	7	0	1	2	2	1	0	11	5	3	0	8	5
	San Francisco	0	0	5	7	4	10	1	1	3	3	2	1	6	4	1	3	7	5
	Los Angeles	1	0	1	1	3	5	0	0	3	0	0	0	2	4	5	3	6	4
Korean	Los Angeles	0	0	0	6	1	3	0	0	2	2	0	0	6	3	0	0	7	1
Filipino	Manila	0	0	1	1	2	5	3	2	1	1	1	0	3	2	1	1	6	4
	Hawaii	0	0	3	0	7	18	1	1	2	1	1	1	8	9	3	3	4	4
	Los Angeles	0	0	2	3	4	12	1	0	2	2	2	1	5	3	1	1	7	3
Malay	Singapore	1	0	2	2	1	3	1	0	1	1	1	0	3	3	0	0	4	4
Indian	Singapore	1	0	1	1	3	4	0	1	0	1	1	0	2	2	1	1	4	3
	Fiji	0	0	1	0	0	3	0	0	2	2	1	1	2	1	0	4	4	4
Polynesian	New Zealand Maori	1	0	12	6	3	3	1	2	2	3	4	1	7	4	7	6	11	6
	Hawaii	1	1	4	3	7	9	1	2	6	1	1	0	9	4	6	4	9	4
Melanesian	Fiji	1	0	2	0	1	4	2	1	4	2	2	0	3	1	2	0	2	1
	New Caledonia	1	1	2	3	1	11	1	2	0	0	1	0	2	1	1	0	7	2
Latin American	Cali, Colombia	0	0	6	3	2	5	1	1	3	3	3	1	5	4	3	2	7	6
	Lima, Peru	1	0	1	1	2	3	1	0	2	1	0	0	4	4	1	1	4	4
	San Francisco	1	1	4	3	2	6	1	1	2	2	2	1	8	5	4	3	6	5
	Los Angeles	1	0	5	3	2	6	1	1	2	1	2	1	5	4	3	2	8	5
Alaska Native	Alaska	1	1	3	2	5	7	0	0	1	3	0	0	12	2	3	0	2	2
Black	San Francisco	1	0	5	4	2	3	0	1	3	2	4	1	6	3	7	4	9	6
	Los Angeles	0	0	5	3	2	3	1	1	1	1	2	1	5	4	7	5	6	5
European	New Caledonia	0	2	2	2	1	6	1	0	1	0	0	2	2	2	1	0	6	2
	New South Wales	1	1	6	4	1	3	1	1	2	1	3	3	9	7	3	3	8	8
	New Zealand	1	1	7	5	1	3	1	1	2	1	3	2	7	5	3	2	8	5
	Hawaii	1	0	6	3	2	6	1	0	2	1	3	2	10	8	3	1	12	8
	British Columbia	1	1	7	5	1	3	1	1	2	1	2	2	9	7	3	2	8	5
	Seattle	1	1	1	0	2	4	1	1	2	2	3	2	9	7	3	2	10	5
	San Francisco	1	1	8	5	3	6	2	1	2	2	4	2	9	7	3	2	10	6
	Los Angeles	1	1	7	5	3	7	1	1	3	2	4	2	8	7	3	2	11	7

TABLE 3.—*Sources of data on incidence rates*[a]

Area	Source person(s)	Registry/organization
Osaka	A. Hanai	Center for Adult Diseases
Hawaii	L. N. Kolonel	Cancer Center of Hawaii, Honolulu
San Francisco	D. F. Austin	Resource for Cancer Epidemiology
Los Angeles	T. M. Mack H. R. Menck	Cancer Surveillance Program
Shanghai	Yu-Tang Gao	Shanghai Cancer Institute
Hong Kong	J. H. C. Ho	Queen Elizabeth Hospital, Kowloon
Singapore	H. P. Lee K. Shanmugaratnam	Singapore Cancer Registry
Manila	H. C. Baltazar	Central Tumor Registry
Fiji	K. Singh	Fiji Cancer Registry
New Zealand	F. H. Foster J. Fraser	National Health Statistics Centre, Wellington
New Caledonia	B. E. Henderson	South Pacific Commission Cancer Registry
Cali	C. Cuello	Cali Cancer Registry
Lima	L. Olivares	Lima Cancer Registry
Alaska	A. P. Lanier	Center for Disease Control, Anchorage
New South Wales	J. M. Ford	Central Cancer Registry, Sydney, Australia
British Columbia	R. P. Gallagher M. McBride	Cancer Control Agency of British Columbia
Seattle	D. B. Thomas	Cancer Surveillance Program

[a] The data presented in this Symposium were collected by the scientists listed above. When quoting data from a given registry, authors will wish to reference that fact. For example: Lanier AP: Cancer incidence in Alaska Natives: 1978–82. *In* Menck HR, Henderson BE: Cancer incidence in the Pacific Basin. Natl Cancer Inst Monogr 69:105–111, 1985.

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SESSION III

Progress in Cancer Research in the Pacific Basin

Correlations of Values of Micronutrients in Sera With Gastric Pathology [1, 2]

William Haenszel, [3] Carlos Cuello, [4] Pelayo Correa, [5] Alfredo Lopez-S, [6] Guillermo Zarama, [7] *and* Diego Zavala [5]

ABSTRACT—Sera were collected in a high-risk area for stomach cancer in Colombia from 857 residents who had been gastroscoped. The levels of 6 micronutrients (retinol, beta-carotene, ascorbic acid, vitamin E, prealbumin, retinol-binding protein) were measured and the mean values correlated with the presence of gastric pathology thought to represent precursors of stomach cancer. Two micronutrients showed important variations in mean levels by gastric pathology: beta-carotene and vitamin E. Beta-carotene levels were low in patients with dysplasia, but no differences were detected for retinol levels.—Natl Cancer Inst Monogr 69: 115-119, 1985.

A population at extremely high risk to stomach cancer residing in the mountainous areas of the Department of Nariño, in southwest Colombia near the border with Ecuador, has been identified (*1*). Gastroscopic surveys of apparently well, noninstitutionalized individuals in the high-risk area have demonstrated an elevated prevalence of CAG and IM in the gastric mucosa (*2*). These 2 lesions have also been known to appear at an earlier age in this population than among residents of other parts of Nariño who have moderately high risks of stomach cancer.

Observations on precursor lesions require gastroscopy and are best done in high-risk populations. A cohort of 2,245 gastroscoped individuals from the high-risk area are being followed prospectively so that we can observe periodically (at intervals of 3–5 yr) changes in the gastric mucosa. The data assembled on the participants include demographic and personal characteristics, family genetic and ethnic background, diet and residence histories, sources of water supply, base-line gastroscopy results, gastric juice findings, and various determinations on urine specimens. The criteria for the classification of gastric pathology have been described (*2*).

From an etiologic model for stomach cancer, developed in part from our studies in Colombia, we (*3*) postulated a sequence of events, including the elevation of gastric pH and an increased bacterial population capable of reducing nitrates to nitrites, leading to the in vivo synthesis of mutagenic and possibly carcinogenic N-nitroso compounds. The importance of food sources of mutagens was reinforced by the discovery of a potent mutagen in the fava bean, a staple item in the diet of the high-risk area of Nariño (*4, 5*). Results of epidemiologic studies also suggested protective dietary effects. Investigators (*6–10*) who conducted case–control studies in diverse populations have consistently stated that stomach cancer patients eat lettuce less frequently than do controls; lettuce is a good source of beta-carotene and of vitamin E and ascorbic acid, which can block the formation of N-nitroso compounds. Correa et al. (*11*) detected, among other findings during a food consumption survey in 4 Nariño villages at varying levels of stomach cancer risk, that the villagers consumed a lower intake of beta-carotene in the high-risk communities. They suggested that protective diet effects be explored in more detail in the Nariño cohort, so that direct observation of serum vitamin levels could be related to information on precursor lesions and not limited to cancer as an end point.

MATERIALS AND METHODS

Sera were collected from 857 members in the study cohort and sent to the laboratory of Dr. Lopez at the Louisiana State University Medical Center, New Orleans, where the serum levels of vitamin A (retinol) and E, ascorbic acid, beta-carotene, prealbumin, and retinol-binding protein were measured. The choice of the first 4 indices was suggested by results of epidemiologic studies of several sites that described case–control differences in the consumption of foods rich or poor in these micronutrients. Prealbumin and retinol-binding protein determine the ability of the body to transport retinol in the blood stream.

Fifteen-milliliter samples of venous blood, collected without anticoagulant, were protected from light, placed in a covered box, allowed to clot for 2 hours under refrigeration, and then were centrifuged for 15 minutes at 3,000 rpm, after which the serum was removed and transferred to amber screw-cap vials. An aliquot of 1.0 ml was used in the field for preparation of a protein-free filtrate for ascorbic acid determination as indicated below. All samples were shipped by airline carrier in a cooler containing Dry Ice to the central laboratory in New Orleans within 3 weeks of the date of collection.

A protein-free filtrate for ascorbic acid determination was prepared with 5% trichloroacetic acid in the field immediately after the serum was obtained. The protein-free supernatant was transferred to a screw-cap tube and shipped to New Orleans. Determination of ascorbic acid

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ABBREVIATIONS: CAG=chronic atrophic gastritis; IM=intestinal metaplasia.

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was accomplished by the dinitrophenylhydrazine method of Roe and Keuther (*12*). In this method, ascorbic acid is oxidized to dehydroascorbic acid by copper ion. The 2,4-dinitrophenylhydrazine derivative is dissolved in strong sulfuric acid, and the red-orange product is measured spectrophotometrically.

Vitamin E serum samples were treated with ethanol to precipitate protein, and the vitamin was extracted with xylene and determined colorimetrically by the iron chloride method of Hashim and Schuttringer (*13*). Bathophenanthroline was used for estimation of any interfering beta-carotene.

Vitamin A and beta-carotene were determined by the method of Neeld and Pearson (*14*); proteins are precipitated with ethanol, and beta-carotene and vitamin A are extracted with petroleum ether. The beta-carotene concentration is determined by measurement of the absorption of the petroleum ether extract at 450 nm. Vitamin A is determined colorimetrically by a reading of the intensity of blue color produced by the addition of trifluoroacetic acid to the petroleum ether residue extract obtained by evaporation under nitrogen. A correction is made for the amount of beta-carotene present because carotene contributes also to the total color obtained with trifluoroacetic acid. Retinol-binding protein was measured by the Mancini technique that requires commercial radial immunodiffusion plates of agarose with a monospecific antihuman retinol-binding protein produced in animals. Concentrations of retinol-binding protein are determined after a diffusion time of 72 hours. The diameter of the precipitation rings of the unknown is then converted to an estimate of concentration by reference to a standard curve relating precipitation to known concentrations. Prealbumin was measured similarly with the use of commercially available diffusion plates of agarose containing a monospecific human antiserum to prealbumin.

The ideal way for one to proceed is to classify individuals by serologic status, follow them over time, observe changes in gastric pathology, and report the results in the form of rates of transition between disease states. This we plan to do. At present, we are limited to a preliminary analysis of cross-sectional data in the form of associations between serum levels and gastric mucosa pathology in a search for clues on which agents or combinations thereof are protective.

RESULTS

No sex difference was observed in the distribution of gastric pathology (table 1). The prevalence of abnormal gastric pathology increased with age, with the age gradient most pronounced for dysplasia (table 2). The sex and age distributions of gastric pathology in this sample are entirely consistent with earlier observations in the Nariño high-risk population (*2*).

Figure 1 illustrates the variation in mean sera levels of the 6 micronutrients by sex, age, and gastric pathology. To facilitate comparisons among the micronutrients, we adjusted the scale values so that equal distances and slopes reflect equal percentage differences. The CAG and IM have been combined in this presentation because they basically represent the same process: The IM is a component of CAG.

Inspection of figure 1 yields several distinct impressions: 1) Each micronutrient tends to have a specific characteristic profile of variation by sex, age, and gastric pathology; 2) only 2 micronutrients display important variations in mean levels by gastric pathology: beta-carotene and vitamin E; 3) beta-carotene and retinol display distinctly different patterns of variation.

Table 3 provides a capsule summary of patterns of variation by sex, age, and gastric pathology. Table 4 contrasts the sex- and age-adjusted mean values of the 6 micronutrients by gastric pathology. The effect of control for sex and age in these comparisons was minimal, and the adjusted values did not deviate greatly from the crude unadjusted values. The comparisons of micronutrient levels between groups of individuals with dysplastic changes in the gastric mucosa with individuals with normal gastric mucosa are summarized in the last column of table 4. The gradient by gastric pathology is most pronounced for beta-carotene. The contrast for vitamin E, though smaller and exhibiting some irregularity in the data for females, is also statistically significant.

TABLE 1.—*Nariño study population by sex and gastric mucosa pathology*

Pathology of gastric mucosa	Males		Females	
	No.	Percent	No.	Percent
Normal superficial gastritis	209	52.8	255	55.3
CAG	91	22.9	85	18.4
IM	73	18.4	97	21.0
Dysplasia	23	5.8	24	5.2
Total	396	99.9	461	99.9

TABLE 2.—*Nariño study population with abnormal gastric mucosa by age*

Age group, yr	Abnormal[a]		Dysplasia only	
	No.	Percent	No.	Percent
15–29	100	31.3	4	1.3
30–49	157	48.9	19	5.9
≥50	136	63.0	24	11.1

[a] Abnormal gastric mucosa includes CAG, IM, and dysplasia.

TABLE 3.—*Summary of profile of variations in serum levels of 6 micronutrients by gastric pathology, sex, and age*[a]

Nutrient	P:		
	Gastric pathology	Sex	Age
Beta-carotene	<.05	<.001	NS
Retinol	NS	<.001	<.01
Vitamin E	<.01	NS	<.001
Ascorbic acid	NS	"	<.05
Retinol-binding protein	"	<.001	<.01
Prealbumin	"	<.001	<.001

[a] NS = not significant.

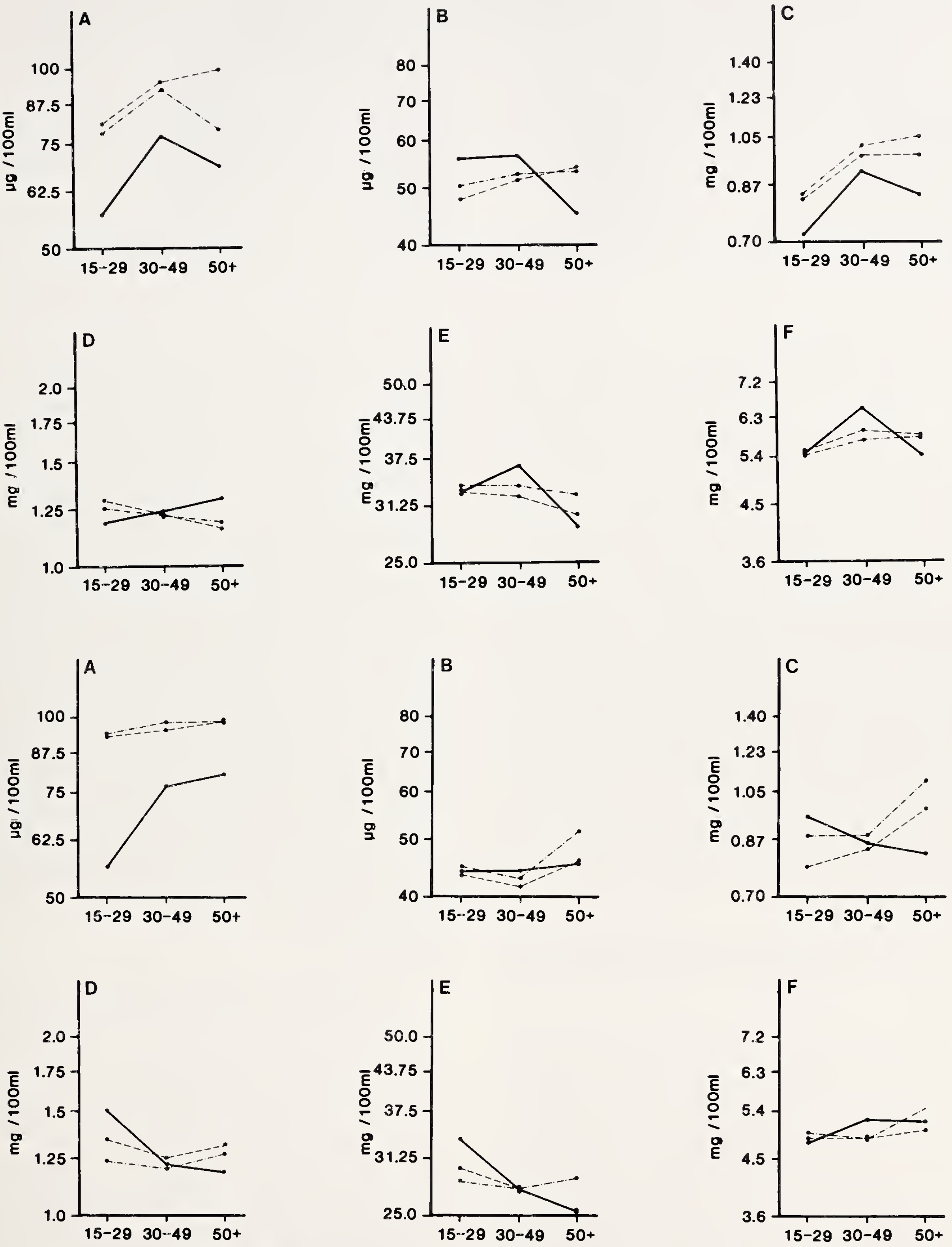

FIGURE 1.—Variation in mean sera concentration of 6 micronutrients by sex, age, and gastric pathology. --- = normal + superficial gastritis; -·-·- = CAG + IM; —— = dysplasia. A = beta-carotene; B = retinol; C = vitamin E; D = ascorbic acid; E = prealbumin; F = retinol-binding protein. *Top* = males; *bottom* = females.

TABLE 4.—*Mean serum levels (adjusted for age and sex) of 6 micronutrients for individuals with normal and abnormal gastric mucosa*[a]

Nutrient	Normal and superficial gastritis (1)	Abnormal mucosa CAG + IM (2)	Abnormal mucosa Dysplasia (3)	Ratio of (3)/(1)
Beta-carotene, μg	92.85±2.08	90.69±2.41	71.31±7.01	0.77
Retinol, μg	46.55±0.63	48.46±0.73	45.97±2.11	0.99
Vitamin E, mg	0.89±0.02	0.94±0.02	0.79±0.05	0.89
Ascrobic acid, mg	1.26±0.01	1.23±0.01	1.25±0.04	0.99
Retinol-binding protein, mg	5.30±0.07	5.38±0.08	5.37±0.22	1.01
Prealbumin, mg	30.05±0.29	30.78±0.34	30.19±0.96	1.00

[a] Values are means ± SE.

Given the large sampling errors for beta-carotene and the not completely consistent pattern for vitamin E, inferences on the nature of the gradients by pathology stage should be guarded. The protective effect of beta-carotene and vitamin E may be more manifest in the transition from CAG and IM to dysplasia and less pronounced in inhibiting the transition from normal mucosa to CAG. However, judgments on this point should await the assembly of data from a large series and follow-up observations on the cohort that will permit computation of rates of transition between pathology states.

Earlier reports from Nariño described a strong correlation between gastric pathology and gastric juice chemistry, i.e., pH and nitrate and nitrite levels (*15*). The present series confirms and elaborates earlier findings. The question of interest here is whether gastric chemistry is a confounding factor responsible for an indirect association of beta-carotene and vitamin E levels and gastric pathology. This point has been examined for beta-carotene, and the results indicate that the lower beta-carotene levels for individuals with dysplasia persist after control for age at varying levels of gastric chemistry. The inverse relationship between beta-carotene levels and gastric pathology in this data set is not due to failure to control for gastric chemistry.

DISCUSSION

The pathology classification and micronutrient determinations were done independently without investigators' knowledge of the other findings. Thus observer bias may be ruled out.

The divergent findings for beta-carotene and retinol are consistent with earlier conjectures by Peto et al. (*16*) that beta-carotene may have a greater protective effect in reducing cancer risk than does retinol. In a study of patients with lung cancer and hospital and general population controls, Lopez and co-workers (*17*) also found beta-carotene serum levels to discriminate more strongly between patients and controls than did retinol. The serologic data also appear consistent with the findings from a 4-village nutrition survey in Nariño which described a deficit in total vitamin A intake in villagers with a high gastric cancer risk (*11*). The low-risk villagers reported higher consumption of carrots and green leafy vegetables rich in beta-carotene. Beta-carotene appears to be the major component of the intervillage difference in total vitamin A intake. Investigators who conducted case–control studies of diet and stomach cancer in other localities throughout the world have described controls to consume more lettuce and other green leafy vegetables and fruits that are rich in beta-carotene. Peto et al. (*16*) summarized some of these findings in their review paper.

We re-emphasize that the data presented are based on a single examination at a specific time. This approach generates essentially the same type of information conveyed by case–control studies of serology. For the presence of clinical cancer, we substituted a presumed precursor state. The introduction of precursor information is helpful because it makes less tenable the interpretation that the serum levels are a consequence of the disease. Another advantage of precursor information in serology is that it lends itself to a cohort approach and facilitates investigation of the sequence of events in time. Continued surveillance of the Nariño cohort will permit the computation of transitional probabilities between pathology states for groups of individuals classified by micronutrient levels in sera. Although the present data are consistent with other epidemiologic observations in suggesting a protective effect for beta-carotene, more evidence is needed. The cohort observations to be generated in the Nariño study setting can contribute to further elucidation of the biologic properties of beta-carotene.

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Urinary Sodium-to-Creatinine Ratio as an Indicator of Gastric Cancer Risk[1, 2]

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Guillermo Zarama,[6] Edilma de Marin,[4] *and* Diego Zavala[3]

ABSTRACT—The difficulties in the estimation of daily intake of sodium chloride in populations are discussed. Total daily output calculations are hindered by the difficulties investigators encounter in obtaining accurate 24-hour urine collections in field work situations. As an alternative, urinary sodium-to-creatinine ratios were investigated. Such ratios, which do not change significantly with circadian excretion rhythms, are useful indicators of the amount of sodium excreted in the urine. Preliminary observations in Colombian populations at high and low risk of gastric cancer indicated higher sodium excretion in the high-risk group. Loss of sodium by other means, especially perspiration, needs to be estimated in some other way.—Natl Cancer Inst Monogr 69: 121–123, 1985.

Foods high in salt content have been proposed as etiologic factors for gastric cancer (*1–6*). Assessment of salt intake presents methodologic problems because salt is added to or is a natural component of dietary items in proportions usually not known by the person being questioned. Inasmuch as electrolytes are kept at a fine balance in the body, sodium excretion in the urine is a good measure of sodium intake. Precise measures of urinary sodium excretion, however, require several accurate 24-hour sample collections (*7, 8*), which are difficult for field workers to achieve in epidemiologic studies.

Because individuals excrete creatinine at a nearly constant rate per unit of time, the sodium-to-creatinine ratio should provide an index of the rate at which sodium is excreted by the kidneys and thus reflects sodium ingestion. Here we explore the variability of urinary sodium-to-creatinine ratios according to time of collection, personal characteristics, and risk to gastric cancer. Additionally, preliminary data on populations at contrasting risk levels to gastric cancer are presented.

MATERIALS AND METHODS

To study the circadian variations in sodium-to-creatinine ratios, we had collected samples of urine covering a 24-hour period from 34 individuals in three Colombian communities (Buga, Cali, LaCruz). The amounts of sodium and creatinine and the sodium-to-creatinine ratio were recorded for each individual. Separate determinations were made for nocturnal and diurnal specimens. All subjects were supposedly healthy employees affiliated with the health centers and were neither pregnant nor hypertensive. They were chosen because their statements, about the completeness of their 24-hour urine samples could be trusted.

Additionally, morning urine samples were taken from 20 blue collar agricultural workers in the high-risk area for gastric cancer in Nariño (Tuquerres) and 255 in the low-risk area of the Colombian Atlantic coast (Sampues). All specimens were collected in plastic bottles containing 10 ml acetic acid and a "knife point" of thymol as a preservative.

The volumes of all urine samples were recorded, and a 100-ml aliquot of each was kept refrigerated and brought, packed in ice, to the central laboratory. The urine was then diluted to 0.1 volume, and, by a modified Jaffe method, a protein-free filtrate was used for measurement of the creatinine (*9*). Sodium was measured by flame photometry. Each batch was validated with serum pools containing known amounts of creatinine and sodium.

RESULTS

Table 1 summarizes the mean day and night values for 34 individuals. Although the nocturnal values were higher, the departure from unity could readily be accounted for by sampling variations. These sample values for each individual were also correlated, and the regression of nighttime versus daytime estimated. The slopes and SE are shown in the last column of table 1. Use of daytime or nighttime values does not systematically overestimate or underestimate the measures of excretion. This is especially true for the sodium-to-creatinine ratio, the measure of primary interest.

The Colombian data consistently showed lower values of 24-hour creatinine output when compared with data available for other countries. Although data for Belgium show a 24-hour creatinine excretion of 1.8 g (*7*), the Colombian data oscillate around 1.0 g/24 hours. Despite the differences in the absolute amounts of creatinine excreted, the Colombian and Belgian data had similar patterns of variation by age, weight, height, and sex as shown by the regression slope values in table 2.

Table 3 contrasts the findings of alternate approaches to the measurement of sodium excretion in Colombian populations of high (Tuquerres) and low risk (Sampues) to stomach cancer. Both populations represent rural, low socioeconomic class agricultural workers. The first con-

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TABLE 1.—*Mean values of sodium, creatinine, and the sodium-to-creatinine ratio in nocturnal and diurnal 12-hr urine samples*[a]

g/hr	Night	Day	Ratio of night to day	Regression slope
Sodium	0.451±0.03	0.398±0.04	1.13±0.10	1.01±0.096
Creatinine	0.039±0.003	0.033±0.002	1.18±0.12	1.12±0.084
Ratio of sodium to creatinine	11.5 ±1.1	12.06 ±0.6	0.95±0.1	1.00±0.096

[a] Samples were collected from 34 individuals in Buga, Cali, and La Cruz. Values are expressed in means ± SE.

trast is based on direct measurement of sodium excretion in 24-hour samples of 20 individuals in Tuquerres and 8 from Sampues. The second reports the observed mean ratio of grams sodium to grams creatinine in specimens from 20 individuals in Tuquerres and 255 in Sampues; most of the latter samples were taken early in the morning and during an unknown interval. In the third approach, we used the available Colombian data to estimate 24-hour creatinine output adjusted for age, sex, height, and weight in each of the 2 groups; this permitted the conversion of sodium per unit of creatinine to sodium per unit time (24 hr).

The sodium-to-creatinine ratio and the direct measurement of 24-hour samples yielded similar estimates of excess sodium excretion in the Tuquerres population (30–40%). The shift in the sodium ratio from per gram of creatinine to per 24 hours leaves the relative position of the 2 populations unchanged. Only if the groups under study differed markedly with respect to attributes related to creatinine excretion would the comparison be altered. The point of the last computational procedure is that it permits an estimate of the absolute amount of sodium excreted over a defined interval. Note that the estimate given by the ratio and creatinine adjustment approach is in reasonably close alignment with the findings from conventional 24-hour urine samples. Further tests of the ratio methodology are indicated.

DISCUSSION

Our results indicate that urinary sodium-to-creatinine ratios are independent of circadian rhythm variations. Because creatinine is excreted at a nearly constant rate, the ratios represent mostly variation in sodium output. Total daily creatinine excretion was lower in Colombia than in other countries, such as Belgium and New Zealand (*7*). These low values may represent methodologic differences. However, the low values remained after we read aliquots from workers in different laboratories using different standards. This matter is being investigated further. The use of local creatinine values for the calculation of the sodium-to-creatinine ratios results in figures comparable to those of Belgium. These findings suggest the value of these ratios in characterizing populations. Previous studies by Joossens (*7*) have shown that such ratios alone are insufficient to characterize individual patterns of sodium excretion, but individual variations do not invalidate their use for intergroup comparisons.

Our finding of higher sodium-to-creatinine ratios in populations at high risk to stomach cancer, when compared with those at low risk, support their usefulness as tools for epidemiologic investigations. Thus it appears that the excretion of sodium in the urine of the high-risk population of Nariño is higher than in the low-risk population living along the Atlantic coast of Colombia. Whether the difference reflects higher sodium intake is not known now because we do not know the amount of sodium lost by other means, especially as perspiration. Both populations represent agricultural workers who get considerable exercise in their work and presumably perspire considerably. However, differences in climate are marked: Nariño is high (3,000 m above sea level) and cold (average temperature, 10°C), whereas the coastal area studied is low (160 m above sea level) and hot (average temperature, 27° C). Comparison of populations living in similar climates but having contrasting gastric cancer risks should help elucidate the role of salt in gastric carcinogenesis.

It has long been suggested that ingestion of foods high in salt content increases the risk of gastric cancer. In 1959, Sato (*1*) reported a positive correlation between gastric cancer death rates and the use of salted vegetables in Japan. This hypothesis received strong support from case–control studies conducted in Hawaii (*3*), France (*6*), and Japan (*2, 10*). An intercountry correlation between gastric cancer and cerebrovascular accident death rates was de-

TABLE 2.—*Slope values for regression of creatinine excretion (in grams) by age, weight, height, and sex*

Variable	Colombia	Belgium
Age, yr	−0.005	−0.006
Weight, kg	+0.011	+0.013
Height, cm	+0.002	+0.004
Sex[a]	+0.051	+0.146

[a] Male = +1; female = −1.

TABLE 3.—*Estimates of mean daily sodium chloride excretion (in grams) in Tuquerres and Sampues*

Basis for estimate	Tuquerres	Sampues	Ratio
Direct measurement of sodium (g) in 24-hr samples	15.3±0.10	11.2±0.3	1.4
g Sodium/g creatinine	18.7±1.3	14.0±0.4	1.3
g Sodium/24 hr[a]	14.8±1.1	11.3±0.3	1.3

[a] Estimate was based on 24-hr creatinine excretion values which incorporate information on age, sex, height, and weight of the subjects.

scribed by Joossens and Geboers (*5*). Both diseases have been linked to high salt intake. Total daily intake is probably more relevant for hypertensive disease, whereas consumption of foods with high salt concentrations are more relevant for gastric cancer (*4*).

The difficulties encountered by researchers in estimating salt intake in populations are well recognized. Some information was provided by responses to questionnaires addressing the issue of salt preservation of foods in certain populations. From previous studies in Nariño, we (*11*) reported that 52% of the interviewees in high-risk areas for stomach cancer preserved meats by salting, compared with 18% in lower risk areas. Sodium intake can also be estimated by nutrition surveys when investigators attempt to quantitate food intake. In one such survey in Nariño, we (*12*) found that the ratio of sodium to potassium was 3.3 in the village with the highest risk and 1.3 in the one with the lowest. An estimate of salt intake can also be inferred from data on the amount of salt bought in a defined period. Such calculations in Nariño led to an estimate of 23.4 g ingested per family member per day, much higher than reported figures for the United States which range from 6 to 18 g/day (*13*). The above estimates in Nariño did not discriminate between persons with normal gastric mucosa and those harboring precursor lesions.

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Colorectal Cancer in Hawaiian Japanese Men: A Progress Report [1, 2]

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ABSTRACT—Comparisons of Hawaiian Japanese with Japanese living in Japan identify several differences between the 2 populations. The Hawaiian Japanese are heavier and taller; they consume more fat and protein; they have higher levels of serum cholesterol, more frequent fecal mutagens, and more frequent adenomatous polyps and diverticulae. These differences offer indirect support to the concept that the consumption of a Western diet favors the development of coronary heart disease and colon cancer which occur more frequently among the Japanese in Hawaii than in Japan. When assessed directly and prospectively, obesity, the serum cholesterol level, and dietary fat intake are positively associated with coronary heart disease. The serum cholesterol level and dietary fat intake are negatively associated with colon cancer, whereas the body mass index (height/weight^2) is positively related to this tumor in older men. The 2 diseases have shown dissimilar trends in the past 20 years, with coronary heart disease being stable at levels intermediate between the United States and Japan experience, whereas colon cancer has shown a steady increase with rates higher than those of whites in the United States. The differences in risk factors and trends displayed by the 2 diseases indicate that they affect different subsets of the westernized Japanese population. Additional studies are necessary if we are to establish the basis for these differences.—Natl Cancer Inst Monogr 69: 125–131, 1985.

In 1970, Doll et al. (*1*) observed that annual colon cancer incidence rates among men of Japanese ancestry in Hawaii were almost four times greater than the prevailing rates found among their counterparts in Japan (15.3 vs. 4.0/100,000). If we assume that genetic factors were constant, this finding indicates that environmental exposures have strongly contributed to the increased colon cancer risk among migrant Japanese men in Hawaii. This increased risk among the Japanese is accompanied by a similar increase in their susceptibility for several other diseases that are commonly encountered in Western populations, such as CHD, prostate cancer, diverticulosis, and polyposis of the colon.

Because of the observed differences in cancer risk between the Japanese in Hawaii and Japan, the Japan–Hawaii Cancer Study began in 1971 in an attempt toward identification of the environmental factors related to the occurrence of colon cancer as well as other cancers among the Japanese men in Hawaii. They are an ethnically homogeneous group with the heterogeneous exposures of migrants that could increase investigators' chances of identifying potential cancer risk factors, especially in the area of diet and nutrition. Since the start of the study, a number of hypotheses generated by us as well as by others have been explored. This report will summarize some of the results of the study related to these hypotheses.

HYPOTHESES

Relationship of Large Bowel Cancer to Factors Characteristic of Western Society

The Japanese men in Hawaii were compared with an age-matched group of men in Hiroshima, Japan (*2*). The Hawaiian men were taller and more obese than the men in Japan, had higher serum cholesterol levels, more frequent glucose intolerance, and different dietary patterns. They consumed more animal protein, cholesterol, and total fat, but less total carbohydrate, vegetable protein, and alcohol than men in Japan (table 1). Their dietary patterns then are not unlike those of Western societies who experience high colorectal cancer rates. Several studies indicate that colon cancer is positively associated with economic status (*3, 4*); we have indirect evidence that this is true for Hawaii Japanese. In Hawaii, the rank order of family incomes among the dominant racial groups is roughly the same as the incidence of colon cancer, with the highest rates occurring in races with the highest family income (Chinese and Japanese). Therefore, we need to assess this characteristic directly within the Japan–Hawaii Cancer Study cohort and to determine how factors associated with prosperity in a Western society (e.g., sedentary occupation, low levels of physical activity, diet) might account for their high risk of colorectal cancer.

Colon Cancer, Myocardial Infarction, and Diverticulosis

The incidence and mortality rates of CHD among Japanese men in Hawaii are intermediate between those of Japanese men in Hiroshima and U.S. whites (*5, 6*) and have been stable over the past 20 years. In contrast, the Hawaii Japanese colon cancer rates exceed those of U.S. whites and have increased during this same period. The epidemiologic variables that have been positively associated with CHD in other populations (e.g., elevated blood pressure, cigarette use, high serum cholesterol, and high serum glucose levels) are also associated with CHD in Hawaii in the Japanese men (table 2).

Measurement of the serum cholesterol was performed at the time of the first examination (*7*). Subsequently, inci-

ABBREVIATIONS: CHD=coronary heart disease; RR=relative risk(s).

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TABLE 1.—*Mean diet values of Japanese men in Japan and Hawaii from 24-hr recall*[a]

Nutrient	Japan	Hawaii
Calories	2,132	2,274
Total protein, g	76 (14.3)	94 (16.7)
Animal protein	40	71
Vegetable protein	37	24
Total fat, g	36 (14.1)	85 (33.2)
Total carbohydrate, g	339 (63.2)	260 (46.4)
Alcohol, g	28 (8.7)	13 (3.7)
Cholesterol, mg	457	545

[a] *Numbers in parentheses* represent percent of total calories.

dence events of colon and rectal cancer were compared with the control population (table 3). Although CHD has shown a statistically significant direct association with serum cholesterol in this population, the association is inverse with right-sided colon cancer that persists even in men diagnosed 5–9.9 years after examination. The differences in CHD and colon cancer in respect to their recent trends, their rates relative to U.S. whites, and in their association with the serum cholesterol level indicate that the pattern of these diseases is different even though they are both more frequent in the Japanese in Hawaii than in their counterparts in Japan.

A high rate of diverticulosis of the colon is one of the most sensitive indicators that a population has assumed a Western life-style. This conclusion is based on autopsy observations among Japanese in Hawaii and Japan (*8, 9*), as shown in table 4. An unusual feature of diverticulosis among Hawaii Japanese is that it occurs as often in the right as in the left colon. Burkitt et al. (*5*) have suggested that the frequency of diverticulosis is an indirect measure of fiber intake. If so, these data indicate that Hawaii Japanese consume less fiber than those in Japan.

Analysis of the distribution of adenomatous and hyperplastic polyps in Hawaii Japanese autopsy subjects indicates that the adenomatous polyps are most numerous in the right colon and hyperplastic polyps in the sigmoid colon and rectum. Thus hyperplastic polyps are more closely related to the sites of cancer of the large bowel than are adenomatous polyps in this population. The morphology of hyperplastic polyps and the cell kinetics of their cell populations suggest that they result from the hypermaturation of epithelium on the surface of the colon (*10*). The presence of hypermature and functioning absorption cells could facilitate the absorption and concentration of enteric carcinogens.

Large Bowel Cancer and Bowel Transit Times

Comparison of Hawaiian Japanese with Hawaiian Caucasians and with Japanese in Akita Prefecture showed no association of bowel transit time with the risk of colorectal cancer or diverticulosis (table 5). The bowel transit times of Hawaii Japanese were similar to those of indigenous Japanese despite the postmigration increase in the frequency of bowel cancer (*11*). The bowel transit times of Hawaii Caucasians were similar to those reported for British subjects (*5*) and much longer than those of the Hawaii Japanese, although the latter group experience higher rates of colon cancer. However, the same study indicated that the stool weight was heaviest in the low-risk indigenous Japanese. This is indirect support for the concept that fiber may play a protective role in carcinogenesis in the colon.

Colorectal Cancer and Degraded Bile Acids

It has been proposed that persons with high levels of degraded (secondary) bile acids in their feces are at high risk for colorectal cancer (*12*). The Japanese in Hawaii have shown higher concentrations of deoxycholic acid (a degraded bile acid) in their fecal specimens than did people in Akita, Japan (*13*), who are at low risk (table 6). The findings for the other bile acids were unremarkable or inconsistent with the hypothesis based on the findings

TABLE 2.—*Summary of multivariate analyses relating risk factors to total CHD and to different manifestations of CHD, Honolulu Heart Study*[a]

Risk factor	Total CHD	Fatal CHD	Nonfatal myocardial infarction	Acute coronary insufficiency	Uncomplicated angina pectoris
Age	+++	++	0	0	+
Systolic blood pressure	+++	+++	+++	+++	0
Body mass index	0	0	0	0	0
Physical activity index	+[b]	0	0	0	0
Hematocrit	0	0	0	0	0
Serum					
Cholesterol	+++	+	+++	0	0
Triglyceride	0	0	+	0	0
Uric acid	++	++	0	0	+
Glucose	+++	+++	0	0	0
Vital capacity/height	++[b]	0	+[b]	0	0
Cigarette smoking	+++	+++	+++	++	0
Alcohol consumption	+++[b]	+++[b]	+++[b]	0	+[b]

[a] 0=no significant association; +=significant association with $P<.05$; ++=significant association with $P<.01$; +++=significant association with $P<.001$.

[b] This represents an inverse association.

Table 3.—*Age-adjusted mean levels of serum cholesterol among colon cancer patients by subsite of tumor within the colon*[a]

Colon subsite	No. of patients	Mean level of serum cholesterol, mg/dl	SE	P[b]
Cecum, ascending colon	21	192	8.3	.002
Sigmoid colon	49	216	5.4	.672
Other colon subsites	10	214	12.0	.733
Rectum	54	221	0.4	.455

[a] Of the 7,534 subjects without colon cancer, the mean serum cholesterol level was 218 mg/dl (SE=5.2).

[b] Values are for the significance of the difference between each subsite specific mean and the mean for all subjects without colon cancer.

Table 4.—*Colonic diverticulae and polyps at autopsy among Japanese in Hawaii and Northern Honshu, Japan*

Sex	No. of patients	Adenomatous polyps		Hyperplastic polyps		Diverticulae	
		No.	Percent	No.	Percent	No.	Percent
Hawaii[a]							
Males	125	80	64	99	79	67	54
Females	77	45	58	55	71	38	49
Total	202	125	62	154	76	105	52
Japan[b]							
Males	376	129	34	9	2	1	0.3
Females	293	50	17	9	3	5	1.7
Total	669	179	27	18	3	6	0.9

[a] *See* (*6*).

[b] *See* (*7*).

Table 5.—*Mean bowel transit times and stool weight in 3 populations*

Population	Bowel transit times, hr			Stool weight, g		
	No. of subjects	Time	*P*	No. of subjects	Weight	*P*
Hawaiian Caucasian (1)	25	56.2	(1)/(2)=.001	18	119.7	(1)/(2)=.50
" Japanese (2)	67	34.4	(1)/(3)=.005	47	120.7	(1)/(3)=.01
Akita " (3)	28	33.9	(2)/(3)=.47	17	194.7	(2)/(3)=.001

Table 6.—*Age- and sex-adjusted geometric mean values of bile acids among study subjects with measurable values in Hawaii and Akita*[a]

Bile acids	Geometric mean values, mg/g dry feces		P[b]
	Hawaii	Akita	
Total	8.61 (0.48, 61.18)	7.45 (0.10, 95.30)	.187
Secondary			
Lithocholic acid	1.25 (0.20, 17.31)	1.12 (0.01, 11.03)	.491
Deoxycholic acid	3.64 (0.11, 41.88)	2.18 (0.02, 30.23)	.001
Primary			
Chenodeoxycholic acid	2.16 (0.09, 23.19)	1.74 (0.11, 14.57)	.275
Cholic acid	0.82 (0.01, 35.36)	0.41 (0.01, 24.23)	<.001

[a] *Numbers in parentheses* are minimum and maximum values.

[b] Analysis of covariance was determined with the 2-tailed *t* test.

TABLE 7.—*Age- and sex-adjusted geometric mean values of neutral steroids among study subjects from Hawaii and Akita with measurable amounts*[a]

Neutral steroid	Geometric mean values, mg/g dry feces		P[b]
	Hawaii	Akita	
Cholesterol	7.92 (1.1, 41.7)	4.14 (1.0, 22.1)	<.001
Coprostanol	7.85 (0.1, 50.0)	7.41 (0.1, 32.7)	.720
Coprostanone	1.05 (0.1, 14.1)	1.05 (0.1, 5.0)	.995
Total animal steroids	18.35 (5.8, 52.9)	11.88 (0.1, 32.7)	<.001
Degraded fraction[c]	0.39 (0.01, 1.0)	0.64 (0.03, 1.0)	.001

[a] *Numbers in parentheses* are minimum and maximum values.

[b] Mean values were adjusted by analysis of covariance; the adjusted means were tested for significant difference (2-sided test) in the analysis of covariance.

[c] Degraded fraction of total animal steroids $= \dfrac{\text{coprostanol} + \text{coprostanone}}{\text{total animal steroids}}$.

from other studies which suggested that degraded bile acids increased colon cancer risk (*14*). Comparison of the fecal bile acid production in cohort men could not be correlated with the consumption of Western types of food products, although 2 Japanese foods (pickled turnip and pickled plum) were negatively associated with the level of modified bile salts in the feces (*15*). These results are suggestive, but not strongly supportive, of a relationship between fecal bile acids and colon cancer risk.

Colorectal Cancer and Fecal Neutral Sterols

Table 7 illustrates a comparison of the neutral steroid concentration between Hawaii Japanese and the Japanese in Akita, Japan (*16*). The Hawaii Japanese have higher concentrations of cholesterol and animal steroids in their feces than do people in Akita. Differences were not meaningful between the 2 groups in concentrations of degraded coprostanol and coprostanone. Furthermore, the degraded fraction was greater in Akita than in Hawaii. These latter findings are neither in agreement with other studies nor strongly supportive of a relationship between fecal neutral steroid patterns and colon cancer risk.

Western Life-style, Colonic Microflora, and Fecal Carcinogens

Feces from Japanese living in Hawaii and Akita showed statistically significant differences in the quantities of water- and ether-soluble mutagens when the Ames procedure (*17*) and the *Escherichia coli rec*$^-$ system (*18*) were used in tests. The presence of direct-acting mutagens in the feces of Hawaii Japanese might account for the higher risk of colon cancer among them (table 8).

Examination of tissue homogenates from the colonic mucosa by the Ames procedure has yielded site-specific mutagens, some of which are nitroso compounds. A total of 9 mutagens have been identified, 8 detected by TA98 and 1 by TA100. Most of the mutagens were recovered from the sigmoid colon, the most common site of colon cancer in this population; the most common of these is characterized as a direct-acting TA98 mutagen with R_T = 7–86 ± 0.36 mm. None of the colonic mucosal mutagens have been characterized, and we have not determined whether they are of endogenous or exogenous origin. However, the mutagen recovered from the sigmoid colon is a chlorinated compound resembling the drug Indocin. None of the patients from which this compound was recovered had received this drug. Incubation of dog colon mucosa with nitrite and drugs to which colon cancer patients are exposed produces nitrosated mutagens with Sublimaze and Robinul. These mutagens do not have high-performance liquid chromatography patterns matching mutagens encountered in the human tissues.

Fat Intake and Colorectal Cancer Risk

Wynder and Reddy (*19*) proposed that a high fat intake increases the risk of colorectal cancer. A comparison of

TABLE 8.—*Percentage distribution of fecal mutagens in Japanese and Hawaii Japanese*

Mutagen type	Akita Prefecture		Honolulu		P[a]
	No.	Mutation ratio	No.	Mutation ratio	Mutation ratio
		≥2.0		≥2.0	≥2.0
Detected by TA98					
Direct acting	118	0.84	136	9.6	.0058
Responsive to S-9 preparation	118	0.84	136	8.1	.016
Detected by TA100					
Direct acting	118	0.85	134	0.7	NS
Responsive to S-9 preparation	103	0.97	130	1.5	NS
Detected by *E. coli rec*$^-$ (water-soluble mutagen)	158	20.8	171	45.6	0.00003

[a] NS = not significant.

TABLE 9.—*Adjusted RR of colon and rectal cancer by quintile of saturated fat intake*

Saturated fat intake, g/day	No. of men			Colon cancer		Rectal cancer	
	Controls	Colon cancer	Rectal cancer	RR[a]	95% Confidence interval	RR[b]	95% Confidence interval
>84.5	1,276	15	11	.49	0.27, 0.91	1.51	0.65, 3.54
64.2–84.5	1,284	14	14	.44	0.24, 0.82	1.78	0.80, 3.94
49.0–64.1	1,284	16	12	.46	0.25, 0.82	1.30	0.58, 2.92
33.1–48.9	1,286	21	10	.59	0.34, 1.00	1.02	0.43, 2.37
<33.1	1,289	40	12	1.00		1.00	
Total	6,419	106	59		P=.035[c]		P=.222[c]

[a] Using logistic regression model, we adjusted for age at examination.

[b] Using logistic regression model, we adjusted for age at examination and alcohol intake (grams ethanol/day).

[c] Test was for linear trend in the values of $\log_e [\text{risk}/(1 - \text{risk})]$, known as the logit of risk.

diets in Hiroshima, Japan (low risk for CHD and colorectal cancer) and Honolulu Japanese (high risk for CHD and colorectal cancer) shows a much higher annual fat consumption in Hawaii but equally striking differences in the amounts of protein and carbohydrates (table 1). When assessed directly in the Honolulu men, CHD and colon cancer differ in respect to fat intake. The incidence and mortality rates for CHD are positively associated with fat intake when this is expressed in percent of calories. In regard to colon cancer, the negative association is statistically significant with fat intake, whether expressed in grams/day or as a percent of caloric intake (tables 9, 10). However, a weak positive association of fat intake with rectal cancer is observed, which is additional evidence that the Hawaii Japanese with CHD and colon cancer constitute different subsets of the westernized Japanese population.

Vitamins and Colorectal Cancer Risk

Measurement of the level of beta-carotene (provitamin A), retinol, and tocopherol in serum obtained before the diagnosis of the 5 most common cancers in the cohort fails to reveal a protective effect against colon or rectum cancer from any of these substances (table 11). This result contrasts with a negative association of lung cancer risk with the serum beta-carotene level. The ratio of the serum vitamin E level to the fasting triglyceride level was calculated for 5 common cancers in this cohort of men and was significantly lower only for colon cancer (table 12), which probably reflects the high fasting serum triglyceride levels in men who subsequently developed colon cancer.

Overnutrition, Obesity, and Colorectal Cancer Risk

The relation of body mass index or weight/height^2 is presented in table 13. Colon cancer had a positive association with the body mass index, although this was not statistically significant. When separated into 2 groups based on age (<55 or ≥ 55 yr), we observed a positive association with colon cancer in the older men. We also noted a positive association between weight gain from age 25 to 45–68 years and colon cancer risk in men who were over 55 years of age at the time of examination. These findings, taken in conjunction with the finding of both low fat and caloric intakes by cohort men who developed colon cancer, suggest that obesity resulting from a surplus of energy consumed over energy utilized has a greater influence on colon cancer risk that the types or amounts of individual nutrients consumed.

IMPLICATIONS FOR FURTHER STUDIES

The findings of the Japan–Hawaii Cancer Study suggest the following areas of epidemiologic research that will yield clues to the origin of colon cancer: 1) review of 24-diet recall questionnaires for assessment of fiber intake, with the use of updated definitions of fiber; 2) a closer look at subsites of colon cancer for identification of epidemiologic variables that can be associated with specific

TABLE 10.—*Adjusted RR of colon and rectal cancer by quintile of percentage of calories from saturated fat*

Percentage of calories from saturated fat, %	No. of men			Colon cancer		Rectal cancer	
	Controls	Colon cancer	Rectal cancer	RR[a]	95% Confidence interval	RR[b]	95% Confidence interval
>31.36	1,280	13	13	.44	0.23, 0.83	2.30	0.94, 5.64
25.66–31.36	1,283	19	13	.61	0.35, 1.08	2.08	0.86, 5.01
20.66–25.65	1,285	22	12	.70	0.41, 1.21	1.83	0.75, 4.46
15.00–20.65	1,283	17	12	.51	0.28, 0.91	1.60	0.66, 3.87
<15.00	1,288	35	9	1.00		1.00	
Total	6,419	106	59		P=.014[c]		P=.081[c]

[a] Using logistic regression model, we adjusted for age at examination.

[b] Using logistic regression model, we adjusted for age at examination and for alcohol intake (grams ethanol/day).

[c] Test was for linear trend in the values of $\log_e [\text{risk}/(1 - \text{risk})]$, known as the logit of risk.

TABLE 11.—*Median values of serum beta-carotene, retinol, and vitamin E among cancer patients and controls*[a]

Cancer site	No.	Beta-carotene, μg/dl		Retinol, μg/dl		Vitamin E, μg/ml	
		Median	*P*	Median	*P*	Median	*P*
Lung	74	20.0	<.005	63.8	>.50	12.8	>.50
Stomach	70	22.8	>.10	60.4	>.50	12.2	>.50
Colon	81	23.5	>.30	62.1	>.50	12.2	>.50
Rectum	32	27.8	>.50	58.8	>.50	11.6	>.40
Bladder	27	29.0	>.50	57.5	>.50	12.7	>.50
Controls	302	29.0		59.6		12.3	

[a] *P* indicates significance of the difference between each site-specific distribution and the distribution for controls, by the nonparametric multiple comparisons procedure of Dunn. *See* (*20*).

TABLE 12.—*Median values of fasting serum triglycerides, serum vitamin E levels, and vitamin E:serum triglycerides*

Patients with cancer of:	No.	Serum triglycerides, mEq/liter	Serum vitamin E, μg/dl	Vitamin E:triglycerides
Colon	27	6.0[a]	12.53	2.07[b]
Rectum	13	5.0	11.60	2.03
Stomach	30	4.6	12.80	2.69
Lung	40	5.8	12.55	2.31
Bladder	13	3.8	13.60	2.71
Controls	102	4.2	12.80	2.95

[a] $P<.05$

[b] $P<.005$ (determined by the nonparametric multiple comparisons procedure of Dunn).

TABLE 13.—*Age-adjusted cancer incidence rates/1,000 men by quintile of body mass index at time of examination*

Cancer site	No.	Body mass index, kg/m^2					*P*[a]
		14.31–21.25	21.26–23.02	23.03–24.60	24.61–26.31	26.32–44.59	
Stomach	104	26.4	15.8	10.3	4.2	12.3	<.001
Colon	101	12.0	11.6	15.7	12.9	17.4	.167
Prostate	96	11.4	9.8	15.4	13.3	14.2	.241
Rectum	63	6.4	11.8	10.9	6.2	5.8	.294
Lung	101	16.8	12.0	12.3	14.9	11.6	.382
Other sites	181	26.7	26.0	19.5	27.0	22.3	.488
All sites	646	91.3	80.5	78.2	73.1	75.9	.086

[a] Test was for linear trend (from Mantel-Haenszel extension test).

segments of the colon; and 3) assessment of the impact of physical activity and obesity on colon cancer risk.

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Vitamin A and Cancer Incidence in a Retirement Community [1, 2]

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ABSTRACT—The use of vitamin A supplements and the risk of cancer was examined in a cohort of 11,888 residents of a retirement community near Los Angeles, California. After 2½ years of follow-up, 445 incident cancers occurred in 435 of the study participants. Overall, the relative risk of cancer for supplement users versus nonusers was 1.0. In a subset of 32 randomly selected individuals, the 14 supplement users had a significantly higher mean serum retinol level (86 μg/dl) than did the 18 nonusers (74 μg/dl).—Natl Cancer Inst Monogr 69: 133–135, 1985.

Vitamin A and its analogs recently received much attention as possible anticancer agents (*1*). These substances are effective in preventing or delaying the development of tumors in animals treated with carcinogens (*2, 3*). Laboratory evidence also suggests that vitamin A and its analogs can suppress the malignant behavior of cultured cells transformed by external carcinogens (*4*). The mechanism for this effect is thought to be related to the role of vitamin A in the maintenance and growth of epithelial cells because vitamin A deficiency leads to cell dedifferentiation and squamous metaplasia (*5*). It has also been suggested that the principal vitamin A precursor, beta-carotene, because of its antioxidant properties, may itself be an anticancer agent (*1*).

We are testing the hypothesis that vitamin A supplements or a high dietary consumption of vitamin A or beta-carotene, or both, may lower cancer risk in humans; we are using a cohort of residents of a retirement community.

MATERIALS AND METHODS

In June 1981, we mailed a detailed health questionnaire to each of the 18,418 permanent residents of a retirement community near Los Angeles, California. In June 1982, the same questionnaire was mailed to the 752 persons who moved into the community since the first mailing. Residents of this community are mainly white, affluent, and highly educated. They have a median age of 75 years, and about two-thirds are women. After three mailings and follow-up phone calls, 11,888 residents completed the health questionnaire. Respondents had demographic characteristics comparable to the community as a whole.

Among other factors, the health survey elicited information on use of vitamin supplements, including details on dose and frequency, and on frequency of consumption of foods rich in vitamin A or beta-carotene. Frequency of consumption was a multiple choice item: “rarely or never,” “a few times per year,” “about monthly,” “a few times per month,” “a few times per week,” and “daily or almost daily.” Seasonal use was also taken into account.

Ongoing follow-up of residents for cancer and other disease development is being accomplished by several means: 1) We screen discharge summaries of 3 local hospitals. On the basis of responses to a survey question on preferred hospitals, we estimate that this surveillance should ascertain about 90% of all hospitalizations. An additional 5% of cancer diagnoses should be obtained by our Los Angeles County Cancer Surveillance Program, a population-based tumor registry of Los Angeles County. 2) Every other year, we conduct a follow-up mailing to each of the original participants. We are in the process of completing our first such follow-up and thus far have received responses from over 80%. 3) We ascertain death certificates of community residents from the local health department.

The RR of cancer for vitamin supplement users versus nonusers was calculated as the overall cancer rate in users divided by the cancer rate in nonusers.

We measured serum retinol levels in 32 randomly selected participants in our cohort study, 11 males and 21 females, with a mean age of 74 years. Serum retinol levels were assayed according to standard methods (*6*). We tested the difference in levels between vitamin A supplement users and nonusers by a one-sided Wilcoxon rank sum test.

RESULTS

Vitamin A supplements are regularly used by 44% of the participants in this study; the median intake is 10,000 IU daily. Slightly more women than men in this community use vitamin A supplements (46 vs. 41%) but their use is unrelated to age or length of residence in the community. We looked for other correlates of vitamin A supplement use. Supplement users tend to use other health services more than do nonusers. For example, they tend to see their doctors more regularly, to use recommended disease screening procedures more consistently, and to take other elective drugs, such as laxatives or over-the-counter analgesics, more frequently. However, none of the differences between users and nonusers were large (table 1).

ABBREVIATION: RR = relative risk(s).

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TABLE 1.—*Percent frequency of certain characteristics by use of vitamin A supplements*[a]

Characteristics	Users	Nonusers
Sex: Male	34	38
Have regular physician	92	90
See physician yearly or more frequently	62	58
Had blood pressure taken in previous year	93	91
Ever had occult blood test	49	44
Use nonprescription drugs regularly	41	37
Use laxatives regularly	29	25
Currently smoking	11	11
Have special diet	37	33

[a] No. of users = 5,245; nonusers = 6,617. Mean age was 75 yr, and mean No. of yr in community = 8 yr for both groups.

TABLE 3.—*Incident cancers and RR for carrot eaters by site*

Cancer site	No. of cancers in patients and frequency of carrot consumption		RR for more vs. less use
	Few times/ week or more often	Monthly or less often	
Stomach	6	4	1.2
Colon	33	40	.7
Rectum	11	4	2.2
Lung	17	13	1.0
Female breast	46	34	1.0
Corpus uteri	13	15	.7
Prostate	35	34	.9
Bladder	14	26	.4
All sites	220	213	.8

To date, 445 incident cancers have occurred among 435 of the participants in this study. The most common sites for occurrence of these cancers are shown in table 2. The relatively low number of lung cancers is consistent with the low smoking rates in this community (8% of men and 13% of women currently smoke cigarettes). Of the participants with cancer, 43% were regular users of vitamin A supplements. Overall, the RR of cancer for supplement users versus nonusers was 1.0. The RR for supplement users for some of the numerically most important cancers in the community are also given in table 2. Although the risks vary, probably because of the small numbers of some cancers, we have little evidence thus far that use of vitamin A supplements decreases risk of cancer in this community.

We have not evaluated cancer risk related to dietary intake of vitamin A and beta-carotene based on the food frequency section of the questionnaire. However, we recently conducted a study in this community to assess shorter methods of estimating vitamin A intake (*7*). Although this work further demonstrated the important contribution of supplemental vitamin A intake to the total, it also demonstrated, through the use of multiple regression equations, that carrot consumption alone is a useful predictor of total dietary vitamin A intake. Table 3 presents the RR of cancer with carrot consumption as an index of total dietary vitamin A intake. Risk is compared in residents consuming carrots a few times per week or more often with those who are less regular carrot eaters. For most sites, the RR is near 1.0.

TABLE 2.—*Incident cancers and RR for vitamin A supplement users by site*

Cancer site	No. of cases	No. of supplement users	RR for supplement users
Stomach	10	6	1.9
Colon	74	36	1.2
Rectum	15	6	.8
Lung	30	12	.8
Female breast	80	40	1.2
Corpus uteri	28	16	1.6
Prostate	70	27	.9
Bladder	41	15	.8
All sites	435	189	1.0

Fourteen of the 32 randomly selected study participants for whom serum retinol levels were measured used vitamin A supplements regularly. They had a median daily intake (consumed by 8 persons) of 10,000 IU daily (range 1,250–20,000). Their mean serum retinol level was 86 μg/dl compared with 74 μg/dl for the 18 nonusers, a statistically significant difference ($P = .035$).

DISCUSSION

Several lines of evidence suggest that vitamin A (retinol) may be an effective anticancer agent in man. Prospective studies from Oxford, England (*8*), and Evans County, Georgia (*9*) reveal significantly lower serum retinol levels in apparently healthy individuals who subsequently developed cancer than in those who did not. The Oxford study, conducted by Wald and colleagues (*8*), collected blood samples on 16,000 men aged 35 to 64 years who attended a health screening clinic in 1975–78. Serum retinol levels of the 86 men who developed cancer by the end of 1979 were compared with those of 172 control men of similar age and smoking habits. Not only did the men who developed cancer have significantly lower retinol levels, but the risk of cancer decreased with increasing quintiles of circulating retinol.

In the Georgia study by Kark et al. (*9*), follow-up was 10 years longer than in the Oxford study, but the results were similar. Serum retinol levels were lower in persons with cancer than in controls, and this relationship was present both for smokers and nonsmokers. The middle 3 quintiles of serum retinol were indistinguishable in predicting cancer risk. However, the difference in risk between the 2 extremes was fivefold, and the highest quintile was associated with the lowest risk.

In a recent study of participants in the Hypertension Detection and Follow-up Program, Willett and co-workers (*10*) could not confirm these results. Serum retinol and carotenoid levels of 111 subjects who were free of cancer at the time of sampling but diagnosed as having cancer during the subsequent 5 years were compared with those of 210 cancer-free controls matched for age, sex, race, and time of blood collection. Not only were mean retinol and carotenoid levels similar between the 2 groups, but no differences in risk of cancer were detected between those in the highest and lowest quintiles of circulating retinol and of carotenoids. In fact, the 17 subjects with subsequent lung cancer actually had a higher mean retinol level than their matched controls.

In a series of case-control studies performed in various countries, researchers investigated numerous cancer sites and consistently demonstrated that persons with low intake of beta-carotene or of foods rich in it or vitamin A have a higher risk of cancer than persons with higher intakes. The largest number of studies and the most consistent results relate to lung cancer (*11-14*), but similar results have been observed for cancers of the stomach and prostate (*12*), colon (*15*), esophagus (*16*), and bladder (*17*).

Only in 1 study was the role of vitamin A supplements in cancer development evaluated (*18*). In that case-control study, men who took vitamin A supplements had a significantly lower risk of lung cancer than men who did not (RR=.55), but no association was observed in women.

A major concern to us from the outset of this investigation was the widespread belief that, although serum vitamin A levels rise markedly during vitamin A intoxication, i.e., a condition which occurs with supplemental doses as low as 25,000 IU daily (*19, 20*), blood retinol levels are independent of intake in individuals with adequate liver stores and vitamin A intakes in the physiologic range (*21*). Such independence is not true in several other species in which blood retinol levels are proportional to liver stores which, in turn, are directly related to diet (*22*). Our measurements of the serum retinol levels in 32 randomly selected participants in our cohort study suggest that serum retinol levels can be moderately increased by vitamin A supplementation, even in the physiologic range. This gives added credibility to the hypothesis that use of such supplements might alter cancer risk. We are in the process of trying to confirm these results on a larger sample of residents.

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Relationship of Dietary Vitamin A and Ascorbic Acid Intake to the Risk for Cancers of the Lung, Bladder, and Prostate in Hawaii [1, 2]

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ABSTRACT—This report presents preliminary findings from 3 case-control studies in Hawaii in which we are examining the relationship of dietary vitamin A and ascorbic acid intake to the risk for cancers of the lung, bladder, and prostate. All 3 studies involved home interviews of cancer patients and neighborhood controls and use of a quantitative dietary history method. In the lung cancer study, we found an inverse dose-response effect for total vitamin A intake in males only, with an odds ratio of 1.8 ($P < .05$) for the lowest intake quartile relative to the highest; we found no association for ascorbic acid. In the bladder cancer study, we found lower (but not statistically significant) mean intakes of both vitamins in patients compared with controls, with the effect stronger for ascorbic acid. In the prostate cancer study, no effect was detected for total vitamin A or ascorbic acid in men less than 70 years old, but a direct association of vitamin A only with a dose-response gradient was found for men 70 years or older (odds ratio = 1.8; $P < .05$, for the highest relative to the lowest intake quartile). Our findings at present indicate that vitamin A has a protective effect against lung and bladder cancers but not against prostate cancer and that ascorbic acid has a protective effect against bladder cancer as well. In our later analyses, we will examine the possibility that the effects of vitamin A vary with histologic type and that this may account for the lack of an association with lung cancer in women.—Natl Cancer Inst Monogr 69: 137-142, 1985.

Reasons for the wide variations in cancer risk among the ethnic subpopulations of Hawaii have not been identified. However, differences in dietary exposures are likely to be primary factors: in earlier reports, we showed that in ethnic groups correlations were high between intakes of selected foods or nutrients and the corresponding incidence rates for certain prominent cancers (*1, 2*). In this paper, we report some preliminary results on the associations of vitamin A and ascorbic acid intakes with 3 cancer sites (lung, bladder, and prostate), based on case-control studies. These micronutrients have been identified as possible protective factors against cancer (*3*).

MATERIALS AND METHODS

We began the lung cancer study in 1979 to explore reasons for the apparent lack of correlation between smoking patterns and lung cancer incidence among ethnic groups in Hawaii (*4*). For the period 1979-82, cases were identified through the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology and End Results Program, and special surveillance in all major hospitals on Oahu. All diagnoses were histologically confirmed. For each patient, 2 controls were selected by a random-digit dialing procedure and matched on age (±5 yr) and sex. Each subject was interviewed at home by a trained interviewer who administered a quantitative diet history questionnaire; food frequency and quantity were assessed by a photographic method we developed and tested (*5, 6*). The interview protocol included 84 food items that represented approximately 75 and 85% of the food sources of ascorbic acid and vitamin A, respectively, plus supplement use. The questionnaire also included information on smoking, alcohol intake, occupational exposures, and medical history. Of the patients, 276 or 76% were interviewed directly; for the remaining 88 or 24%, a surviving spouse was interviewed as a surrogate. Analysis of the data was by multiple logistic regression; subjects were ranked into approximate quartiles according to level of exposure (intake) and the use of binary indicator (dummy) variables (*7*). Adjustment variables included age, ethnicity, cholesterol intake [included because this variable showed a statistically significant association with lung cancer risk (*8*) and was also significantly correlated with dietary vitamin A intake], occupation (white collar, sales and service, or blue collar), and cigarette smoking (pack-years). Age, cholesterol intake, and cigarette smoking were used as continuous variables; binary indicator variables were created for ethnicity and occupation. Further detail on the methodology of this study can be found in a more complete report (*9*).

The urothelial (primarily bladder) cancer study was also based on case selection from the major hospitals on Oahu and the Hawaii Tumor Registry. At the start of the study, we identified a series of prevalent cases (defined as patients diagnosed during 1977-79 who were still alive and residing in Hawaii). We identified as incidence cases those patients with histologically confirmed cancer that occurred during subsequent years. The case group was limited to Japanese and Caucasian women and men on Oahu and was individually matched to controls on age (± 3 yr), sex, and ethnicity. Controls were selected by a random procedure from lists of subjects identified at the same time through the Health Surveillance Program of the Hawaii

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State Department of Health. This program annually surveys a random sample of approximately 2% of the households in Hawaii (*10*). Each subject was interviewed at home according to a protocol similar to that used for the lung cancer study described above. However, the bladder cancer study was less comprehensive in assessing vitamin A and ascorbic acid intakes (an estimated 70% of food sources, plus supplements) because it included a substantial amount of information on additional dietary items (e.g., coffee, tea, alcohol, artificial sweeteners) and other exposures of interest. No surrogate respondents were included in this study. Analysis of the preliminary data for this report was by multiple covariance analysis (*11*), with adjustment for age and lifetime cigarette use (pack-years).

The prostate cancer study resembled that of lung cancer in the source of cases and method of identification of controls. Whereas random-digit dialing was used for the identification of controls younger than 65 years, a list of randomly selected men who were living on Oahu was obtained from the Health Care Finance Administration for the identification of older controls. The latter source was used because of the inefficiency of random-digit dialing in identifying elderly persons in the population. The case series included prevalent cases (defined as patients diagnosed during 1977–80 who were alive in 1980 and residing in Oahu) and incidence cases (defined as patients newly diagnosed during 1980–83). Controls were matched to patients on age (± 5 yr) and sex but not ethnicity, as described above for the lung cancer study. The interview protocol was also similar to that for the lung cancer study but included additional food items because of other hypotheses being tested; we designed it to include approximately 85–90% of all food sources of vitamin A and ascorbic acid plus supplement use. In addition, the questionnaire included information on smoking, alcohol use, occupational exposures, and medical history. Analysis of the data was by multiple logistic regression as in the lung cancer study; we examined dose response by ranking the subjects into approximate quartiles on exposure (intake) and the use of binary indicator (dummy) variables (*7*). Adjustment variables included age and total fat intake (entered as continuous variables) and ethnicity and marital status (entered by the creation of binary indicator variables).

RESULTS

Lung Cancer

This analysis was based on 364 patients and 627 controls. The findings for total vitamin A intake (retinol and retinol precursors) from foods as well as supplements are shown in table 1. The dose–response effect is clear in the male subjects, and the odds ratio for the lowest intake group relative to the highest (1.8) is statistically significant ($P < .05$). However, no effect of vitamin A intake on lung cancer risk is apparent in the data for the female subjects. The results of similar analyses based on food sources of vitamin A only and on carotene sources specifically are shown in tables 2 and 3. The results are not notably different from those in table 1. The highest risk (odds ratio of 2.2) is seen for the lowest intake quartile in the carotene analysis (table 3). An additional analysis limited to cigarette smokers (data not shown) yielded findings similar to those for the male subjects in tables 1–3. Although ascorbic acid intake (adjusted for vitamin A) showed no statistically significant association with lung cancer risk, an inverse relationship in men was suggested (table 4).

Bladder Cancer

This preliminary analysis is based on 164 patients (75 Japanese and 89 Caucasian) and 314 controls (149 Japanese and 165 Caucasian). The findings for vitamin A are shown in table 5. For total vitamin A consumption and that from supplements alone, the average intake of patients is less than that for controls in both sexes and ethnic groups. For vitamin A consumption from foods alone, the same pattern is seen, except the Japanese male patients consumed more than controls. None of the differences in this table is statistically significant, however. A similar analysis for ascorbic acid intake is shown in table 6. With the exception of the data for males on intake of this vitamin from food sources, the consumption by patients was less than that by controls for all ethnic–sex groups and categories of intake. The case–control differences are greater in the analysis of supplements than for the other 2 categories, but none of these differences is statistically significant.

TABLE 1.—*Total vitamin A intake and lung cancer risk*[a, b]

Weekly total vitamin A intake, IU[c]	Males			Females		
	No.	Odds ratio	95% Confidence interval	No.	Odds ratio	95% Confidence interval
0–59,599	168	1.8	1.1–3.1	79	0.7	0.3–1.6
59,600–91,499	194	1.3	0.8–2.2	79	0.7	0.3–1.7
91,500–134,999	169	1.2	0.7–2.0	69	1.0	0.4–2.4
≥135,000	174	1.0	—	59	1.0	—

[a] All vitamin A activity from retinol and retinol precursors (carotene) in foods plus retinol supplements is included.

[b] Odds ratios were computed by multiple logistic regression with adjustment for age, ethnicity, cholesterol intake, occupational status, and pack-years of cigarette smoking.

[c] Subjects were divided into approximate quartiles.

TABLE 2.—*Vitamin A intake from foods and lung cancer risk*[a, b]

Weekly vitamin A intake from foods, IU[c]	Males			Females		
	No.	Odds ratio	95% Confidence interval	No.	Odds ratio	95% Confidence interval
0–51,799	159	2.0	1.2–3.5	86	0.8	0.3–2.0
51,800–78,099	191	1.4	0.8–2.4	84	1.2	0.5–2.9
78,100–115,199	175	1.6	1.0–2.7	63	1.7	0.7–4.2
≥115,200	180	1.0	—	53	1.0	—

[a] All vitamin A activity from retinol and retinol precursors (carotene) in foods is included.
[b] *See* table 1, footnote *b*.
[c] *See* table 1, footnote *c*.

TABLE 3.—*Carotene intake and lung cancer risk*[a, b]

Weekly carotene intake, IU[c]	Males			Females		
	No.	Odds ratio	95% Confidence interval	No.	Odds ratio	95% Confidence interval
0–37,799	167	2.2	1.3–3.7	80	0.6	0.2–1.5
37,800–58,999	179	1.1	0.7–1.9	81	0.9	0.4–2.1
59,000–92,999	184	1.1	0.7–1.9	74	0.9	0.4–2.0
≥93,000	175	1.0	—	51	1.0	—

[a] All vitamin A activity from retinol precursors in foods is included.
[b] *See* table 1, footnote *b*.
[c] *See* table 1, footnote *c*.

TABLE 4.—*Total ascorbic acid intake (including supplements) and lung cancer risk*[a]

Weekly ascorbic acid intake, mg[b]	Males			Females		
	No.	Odds ratio	95% Confidence interval	No.	Odds ratio	95% Confidence interval
0–1,050	189	1.6	0.8–3.4	77	0.7	0.2–2.2
1,051–1,780	177	1.3	0.7–2.2	72	0.6	0.2–1.5
1,781–3,639	155	0.9	0.6–1.5	63	1.2	0.6–2.4
>3,640	184	1.0	—	74	1.0	—

[a] Odds ratios were computed by multiple logistic regression with adjustment for age, ethnicity, cholesterol intake, occupational status, vitamin A intake, and pack-years of cigarette smoking.
[b] *See* table 1, footnote *c*.

Prostate Cancer

The analysis for this report is based on 418 patients and 771 controls, 56% of whom were at least 70 years old. The analysis for vitamin A intake was done separately for those men aged 70 or older and those 69 or younger. Table 7 presents the results for the younger group. Although decreased risks are suggested for subjects in the highest intake quartiles, none of the odds ratios is statistically significant nor is the overall pattern monotonic. For the older age group (table 8), a much different pattern is seen, i.e., a positive relationship between vitamin A intake and prostate cancer risk. In the total vitamin A analysis, the odds ratio for the highest intake quartile relative to the lowest (1.8) is statistically significant. No evidence of an effect of ascorbic acid intake on prostate cancer risk was observed (table 9).

DISCUSSION

Our findings on vitamin A and lung cancer are generally consistent with those of other investigators (*12–16*). Although the risks were higher in the carotene than in the total vitamin A analysis, we cannot conclude on the basis of this analysis that the apparent protective effect is specific to carotene, as found by Shekelle et al. (*16*) and as suggested by the findings in Chinese women of MacLennan and co-workers (*13*). Also notable is that the risks from the various case–control studies, including ours, and the cohort study of Bjelke (*12*) are in the same range. Only

TABLE 5.—*Vitamin A intake among Japanese and Caucasian patients with bladder cancer and controls*

Ethnic group/sex	No.	Mean daily intake, IU[a]		
		Total	From foods	From supplement
Males				
Japanese				
Patients	52	7,857.9	5,571.1	2,286.8
Controls	105	8,311.9	5,288.0	3,024.0
Caucasians				
Patients	71	9,042.1	6,513.9	2,528.1
Controls	133	9,868.7	7,095.8	2,772.9
Females				
Japanese				
Patients	23	7,211.8	5,309.5	1,902.2
Controls	44	9,192.4	6,191.6	3,000.8
Caucasians				
Patients	18	10,814.8	5,813.2	5,001.5
Controls	32	11,934.6	6,801.6	5,133.1

[a] Values were adjusted for age and lifetime cigarette use (pack-years) by multiple covariance analysis. None of the case-control differences is statistically significant (*P*>.05).

TABLE 7.—*Vitamin A intake and prostate cancer risk in the ≤69-yr age group*[a]

Weekly intake, IU[b]	No.	Odds ratio	95% Confidence interval
Total vitamin A			
0–41,999	133	1.0	
42,000–68,999	125	1.2	0.7–2.0
69,000–102,999	134	1.1	0.6–1.8
≥103,000	129	0.7	0.4–1.2
Food sources only			
0–34,999	132	1.0	
35,000–53,999	129	1.3	0.8–2.2
54,000–77,999	131	1.4	0.8–2.3
≥78,000	129	0.8	0.4–1.4
Carotenes only			
0–12,399	131	1.0	
12,400–19,699	133	1.3	0.8–2.2
19,700–29,299	129	1.1	0.7–1.9
≥29,300	128	0.9	0.5–1.5

[a] Odds ratios were computed by multiple logistic regression with adjustment for age, ethnicity, marital status, and total fat intake.

[b] *See* table 1, footnote *c*.

the study by Shekelle et al. (*16*) stands out in this regard, with about a threefold greater estimate of the risk in their carotene-specific analysis.

Perhaps the most unexpected result of our analysis is the failure to find a comparable protective effect in the female subjects. Most other reports have been exclusively on findings in men, but Gregor et al. (*15*) included men and women in their study and found a result similar to ours. Smith and Jick (*17*) also included men and women in a study of vitamin A pill use and overall cancer risk; they found an increased risk for cancer only among men who did not use vitamin A preparations regularly. Reasons for a possible differential response in the 2 sexes are not apparent, but the influence of hormonal balances on vitamin A metabolism or tissue response is an obvious consideration. Perhaps more likely is the possibility of some histologic specificity to a protective effect by vitamin A.. The distribution of histologic types of lung cancer among men and women differs, with proportionally more adenocarcinomas among women (*18*). To examine this possibility further, we are continuing to select patients for this study to increase the sample sizes for women and for the different histologic subgroups.

The results of serologic analyses for retinol and beta-

TABLE 6.—*Ascorbic acid intake among Japanese and Caucasian patients with bladder cancer and controls*

Ethnic group/sex	No.	Mean daily intake, mg[a]		
		Total	From foods	From supplement
Males				
Japanese				
Patients	52	405.0	131.7	273.3
Controls	105	406.5	127.7	278.8
Caucasians				
Patients	71	419.8	147.9	271.9
Controls	133	574.6	138.7	435.9
Females				
Japanese				
Patients	23	312.8	144.8	168.0
Controls	44	494.0	162.8	331.2
Caucasians				
Patients	18	317.6	142.5	175.1
Controls	32	634.0	143.3	490.7

[a] Values were adjusted for age and lifetime cigarette use (pack-years) by multiple covariance analysis. None of the case-control differences is statistically significant (*P*>.05).

TABLE 8.—*Vitamin A intake and prostate cancer risk in the >70-yr age group*[a]

Weekly intake, IU[b]	No.	Odds ratio	95% Confidence interval
Total vitamin A			
0–42,999	168	1.0	
43,000–64,999	164	1.2	0.8–2.0
65,000–96,999	172	1.2	0.7–1.9
≥97,000	164	1.8	1.1–3.0
Food sources only			
0–37,999	165	1.0	
38,000–54,999	169	1.1	0.7–1.8
55,000–78,999	171	0.9	0.5–1.4
≥79,000	163	1.5	0.9–2.4
Carotenes only			
0–13,999	172	1.0	
14,000–20,499	169	1.2	0.8–2.0
20,500–29,799	164	1.4	0.9–2.2
≥29,800	163	1.3	0.8–2.2

[a] *See* table 7, footnote *a*.

[b] *See* table 1, footnote *c*.

TABLE 9.—*Ascorbic acid intake and prostate cancer risk*[a]

Weekly intake, mg[b]	No.	Odds ratio	95% Confidence interval
Total			
0–799	257	1.0	
800–1,399	295	1.0	0.7–1.4
1,400–3,099	342	1.1	0.8–1.6
≥3,100	295	1.0	0.7–1.5
Food sources only			
0–709	301	1.0	
710–1,109	296	1.1	0.8–1.6
1,110–1,589	300	0.8	0.6–1.2
≥1,590	292	0.9	0.7–1.4

[a] *See* table 7, footnote *a*.

[b] See table 1, footnote *c*.

carotene are still inconclusive. Two early reports based on cancer occurrence in prospective cohorts (*19, 20*) found lower prediagnostic levels of vitamin A in subjects who subsequently developed cancer than in controls. In contrast, Willett et al. (*21*) failed to show an association of serum retinol levels with cancer in an analysis of patients (all sites) and controls in the Hypertension Detection and Follow-up Program, on whom prediagnostic fasting specimens were available. They also found no evidence for an inverse association of cancer with total carotenoids in this study, but the numbers were too few for meaningful site-specific analyses. In a case-control serologic study (*22*), 26 patients with lung cancer had lower mean beta-carotene levels than did 21 controls (105 vs. 125 μg/dl), but, again, the numbers were insufficient for one to draw any firm conclusions. Clearly, as with dietary assessment, more work needs to be done if we are to clarify the relationship of serum vitamin levels to risk for specific sites of cancer. Furthermore, serum carotene only reflects recent, not long-term, intake, and serum retinol is homeostatically controlled at relatively constant levels in the absence of severe depletion of body stores or extreme excess of intake (*23–25*).

We saw little evidence of an effect of ascorbic acid on lung cancer risk. Although we adjusted for vitamin A consumption in examining this relationship, the slight suggestion of a possible inverse association in men could reflect residual confounding. Notably, when we adjusted for ascorbic acid intake in the vitamin A analyses, the inverse association in men persisted to the same extent as shown in tables 1–3, with no association seen for women.

Our findings for bladder cancer suggest the possibility of a protective effect for either or both vitamins. Although the results based on the small numbers of subjects in each category were not statistically significant, consistency was notable across ethnic and sex groups. In this analysis, we did not control for 1 vitamin while examining the other, and, as expected, the 2 are highly correlated in the diet in our population (*1*). Because the results for ascorbic acid were stronger than for vitamin A, one might be tempted to conclude that this is the more likely of the 2 vitamins to be independently associated with risk for bladder cancer. This conclusion is supported by epidemiologic and experimental data that suggest the possibility that N-nitroso compounds play a role in the occurrence of bladder cancer (*3*); ascorbic acid, an antioxidant, can inhibit the formation of these compounds in in vitro and in vivo systems (*26, 27*). On the other hand, an epidemiologic study by Mettlin and Graham (*28*) suggested that vitamin A is also protective against bladder cancer. Thus it is impossible for one to draw any conclusions now as to which of these nutrients, if only 1, may be etiologically related to bladder cancer.

The results of the analyses for vitamin A and prostate cancer are confusing. We separated the subjects into 2 age groups, as did Graham and associates (*29*). In the younger age group, we observed no clear association between vitamin A intake and prostate cancer, whereas in the older men, we found a positive association of total vitamin A intake with prostate cancer risk. In a previous analysis, based on a smaller sample (*30*), this association was stronger (a relative risk of 2.5 for the highest intake quartile). Although we can find no obvious biases in the study to account for this effect in the older men, these results are preliminary, and more complete analyses will be done on the final sample.

In the meantime, we have good reasons to take this finding seriously. Graham et al. (*29*) also reported a direct association between an index of vitamin A intake and prostate cancer risk, particularly in older men, in contrast to their findings for this nutrient in relation to other cancer sites (*14, 28, 31–34*). Experimental evidence has shown that the effect of vitamin A on carcinogenesis in animals can be one of either inhibition or enhancement, depending on the experimental conditions (*3, 35*). Nevertheless, at present it would be premature for us to conclude that vitamin A intake is a risk factor for human cancer of the prostate or other sites.

The data of these 3 studies suggest that vitamin A (without distinction between the preformed and precursor forms) has a protective effect against lung and bladder cancers. Because prostate cancers are adenocarcinomas and a higher proportion of females than males have this histologic type of lung cancer, a possible explanation for the absence of any inverse association in the groups with lung cancer (females) and prostate cancer is that vitamin A has a weaker effect on adenocarcinomas than it does on squamous, transitional, and possibly other epithelial cell types.

Ascorbic acid appears to have no major effect on either lung or prostate cancer risk, but the data do suggest a protective effect against bladder cancer. The best established mechanism for the protective effect is its inhibition of the formation of N-nitroso compounds (*26, 27*). If this mechanism fully explains the role of this vitamin in cancer occurrence, the range of sites involved would be expected to be more limited than that for vitamin A. Sites where both nitrosamines and ascorbic acid have been implicated include the stomach, esophagus, and bladder (*3*). However, Wassertheil-Smoller and associates (*36*) suggested its protective effect against cervical dysplasia; if confirmed, this may imply another and perhaps more general mechanism of action of this vitamin as a protective factor against cancer.

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Mortality in Japanese With Life-styles Similar to Seventh-Day Adventists: Strategy for Risk Reduction by Life-style Modification [1]

Takeshi Hirayama [2]

ABSTRACT—Using 16 years of follow-up results of a prospective cohort study for 122,261 men, 95% of the census population, aged 40 years and older in 29 Health Center Districts in Japan as subjects, we compared the age-standardized mortality rates for cancer of each site and other causes of death in Japanese with life-styles similar to those of Seventh-Day Adventists (SDA), i.e., no smoking, no drinking, no meat consumption daily and eating green and yellow vegetables daily, with those of Japanese with opposite life-styles. Compared with the latter Japanese, the risks were one-fifth or less in Japanese with SDA-like life-styles for cancers of the mouth, pharynx, esophagus, and lung, and subarachnoid hemorrhage. Risks were less than one-half for cancers of all sites, stomach, and liver, and for peptic ulcer and heart disease. As a single factor, the addition of daily smoking was observed to elevate the risk most strikingly in Japanese who followed SDA life patterns. Influences of further addition of habits of daily drinking of alcohol and dietary changes were significant for cancers of the esophagus, liver, and bladder and other selected diseases. Strategies for cancer prevention by means of life-style modification, e.g., increased consumption of green and yellow vegetables, were discussed.—Natl Cancer Inst Monogr 69: 143-153, 1985.

It is well known that SDA have a low risk of dying (in comparison to other persons) from various causes of death, including cancer. It is important that we observe if other subgroups in the general population with similar life-styles also have a low risk of dying from such diseases.

A large-scale cohort study on cancer epidemiology has been in progress in Japan. Using the results of 16 years of follow-up, the author studied this issue intensively as well as the effectiveness of various strategies for cancer prevention by life-style modification.

MATERIALS AND METHODS

A large-scale population-based cohort study has been in progress in Japan for 16 years (1966–81). Life-styles of 122,261 men aged 40 years and older residing in 29 Health Center Districts were surveyed and followed; this number represented 95% of the population in October to December 1965.

The study was conducted by home visits to participants by public health nurses and midwives in each health center who were trained for the standardized method of the interview. The form itself was simple and straightforward, and only items easy for participants to answer were included. We provided printed guidelines and made tapes to demonstrate the model inquiries.

Some examples of guidelines were as follows:

1) Area numbers, household numbers, and individual numbers must be recorded as identification items for each person in addition to name, sex, date of birth, and detailed address.

2) For items regarding diet, information on current habits throughout the year is required and not seasonal peculiarities.

3) Criteria for frequency of consumption are: daily = four or five or more times a week; rare = one to three times a month; occasional = in between first 2 criteria; none = two to three times a year (such as at a festival).

Ascertainment of meat and vegetable consumption was satisfactory according to the results of comparisons of the 1965 and 1971 surveys on 7,507 individuals who were randomly selected from tables of the original population (that also were randomly numbered). The rate of agreement by daily consumption was: 91.3% for smoking, 83.6% for drinking, 96.3% for meat, and 99.3% for vegetables. The rate of exact agreement (daily, occasionally, rarely, and never) was 84.8, 58.1, 63.3, and 65.7%, respectively. Thus information on diet was as stable as that of smoking and drinking especially for daily or nondaily category. The one-time assessment of factors, though open to criticism to a certain extent, was considered acceptable and permissible for practical purposes as in most other cohort studies in the literature.

To enable the follow-up of study subjects, we established a system of record linkage between the original risk-factor records and those of the annual census for residence check and death certificates.

Japanese with SDA-like life-styles who daily neither smoke, drink alcohol, nor eat meat, but do eat green and yellow vegetables (group 0010) were selected. The SMR for each cause of death were compared with Japanese with opposite life-styles, i.e., those who smoke, drink alcohol, and eat meat daily, but do not eat green and yellow vegetables daily (group 1101).

Other groups of Japanese were selected with SDA-like dietary patterns but who daily smoke cigarettes (group 1010), drink alcohol (group 0011), eat meat (group 0110), or do not eat green and yellow vegetables daily (group 0000). Groups smoking cigarettes and drinking alcohol

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ABBREVIATIONS: SDA=Seventh-Day Adventist(s); SMR=age-standardized mortality ratio(s); RR=relative risk(s).

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daily (1011) were also selected and compared with the appropriate groups (0010 and 1101).

Lastly, other groups of Japanese with SDA-opposite life-style patterns but who neither smoke cigarettes (group 0101), drink alcohol (group 1100), nor eat meat daily (group 1001), but do eat green and yellow vegetables daily (group 1111) and retain all other habits were selected. They were also compared with the appropriate groups (0010 and 1101).

RESULTS

Little difference was noted in the association of life-style variables in the different prefectures. In other words, consistency of association was striking for most of the variables. An example of the consistent association of meat intake and colon-rectum cancer is shown in figure 1. Therefore, materials for whole areas were used for subsequent analysis.

The statistically significant differences in the SMR for selected causes of death that were found between the risks of Japanese with SDA-like life-styles (group 0010) and those with entirely opposite life-styles (group 1101) are presented in figure 2. The RR of group 0010 to group 1101 are listed in table 1 as are observed person-years and the number of deaths in each life-style category. Thus a switch to an SDA-like life-style would be expected to reduce drastically the risk of selected causes of death, including cancers of many sites.

As shown in tables 2 and 3 and figure 3, each life-style variable has a different effect on the risk of dying. When people with an SDA-like life-style retain all other habits but 1) smoke cigarettes daily, their risks of getting most diseases tends to rise; 2) drink alcohol, their risks for hypertensive heart disease and cirrhosis of the liver are elevated; 3) eat meat, their risks for ischemic heart disease and cancers of the pancreas, esophagus, and lung are also increased; and 4) stop eating green and yellow vegetables, a rise in their risks for peptic ulcer, cirrhosis, and cancer of the esophagus is apparent. An elevated risk in cirrhosis of the liver was striking with daily ingestion of alcohol to an SDA-like life-style. When meat was added to the daily

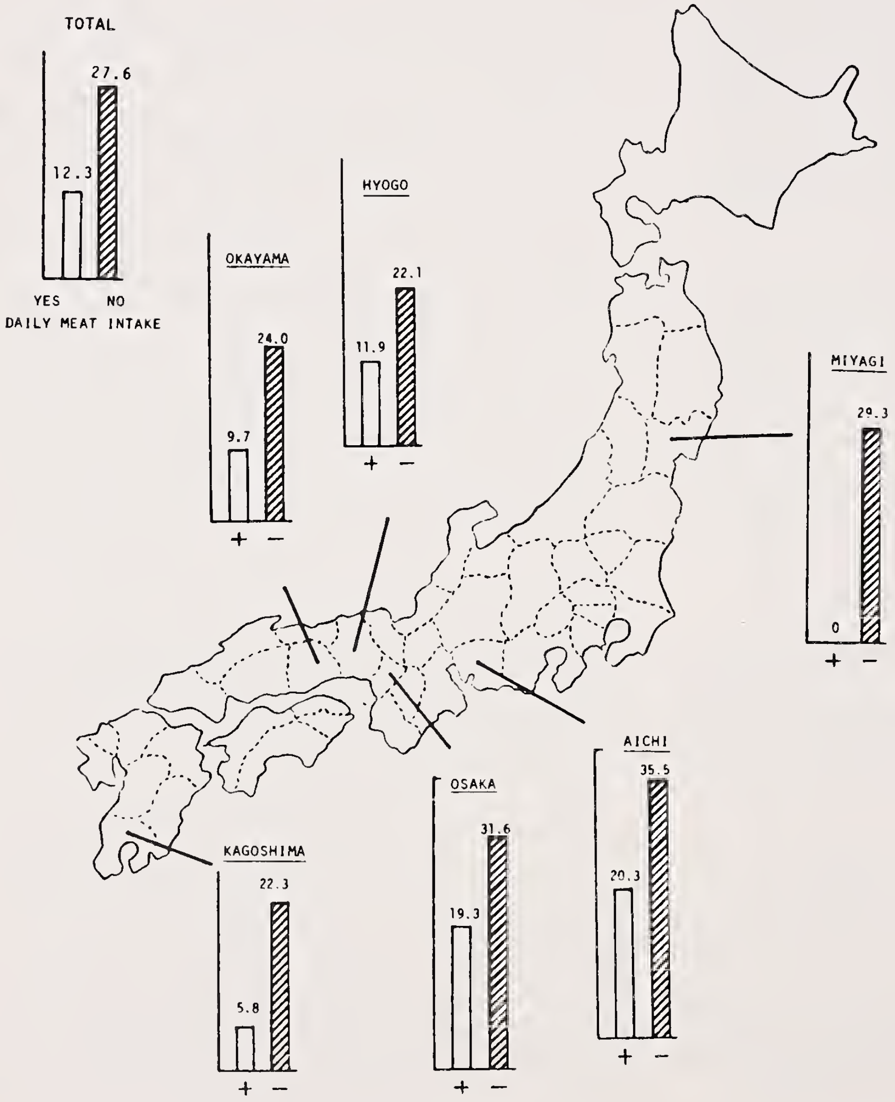


FIGURE 1.—The SMR for cancers of the colon and rectum and meat intake for Japanese males according to the data from a prospective study, 1966–78.

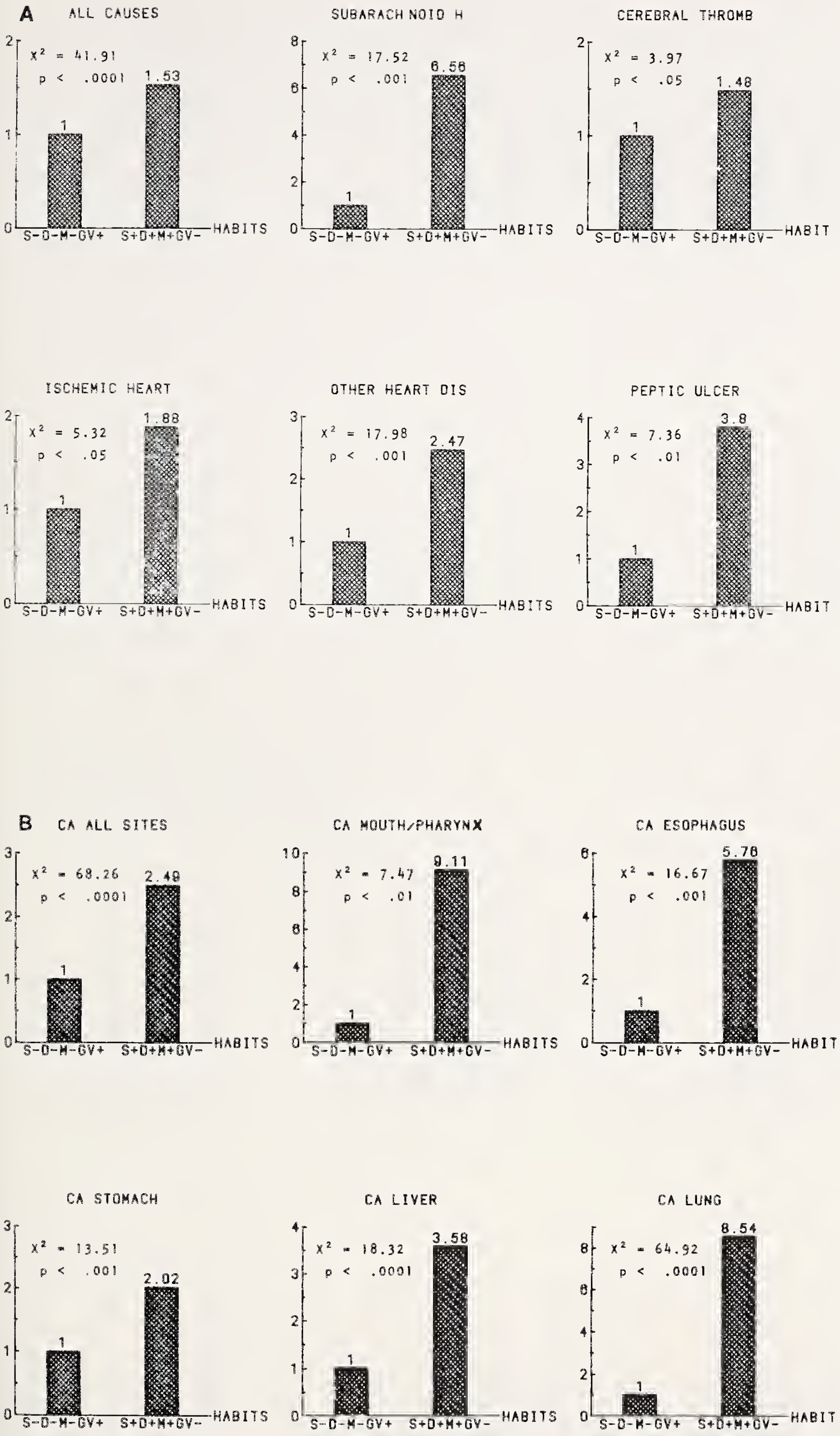


FIGURE 2.—A) Selected causes of death and B) cancer of selected sites in Japanese with SDA-opposite life-styles.

FIGURES 2–5.—The SMR for Japanese according to data from a prospective study conducted during 1966–81. H = hemorrhage; thromb = thrombosis; dis = disease(s); S = smoking; D = drinking (alcohol); M = meat; GV = green and yellow vegetables; ca = cancer; art. = arterio; malig. = malignant.

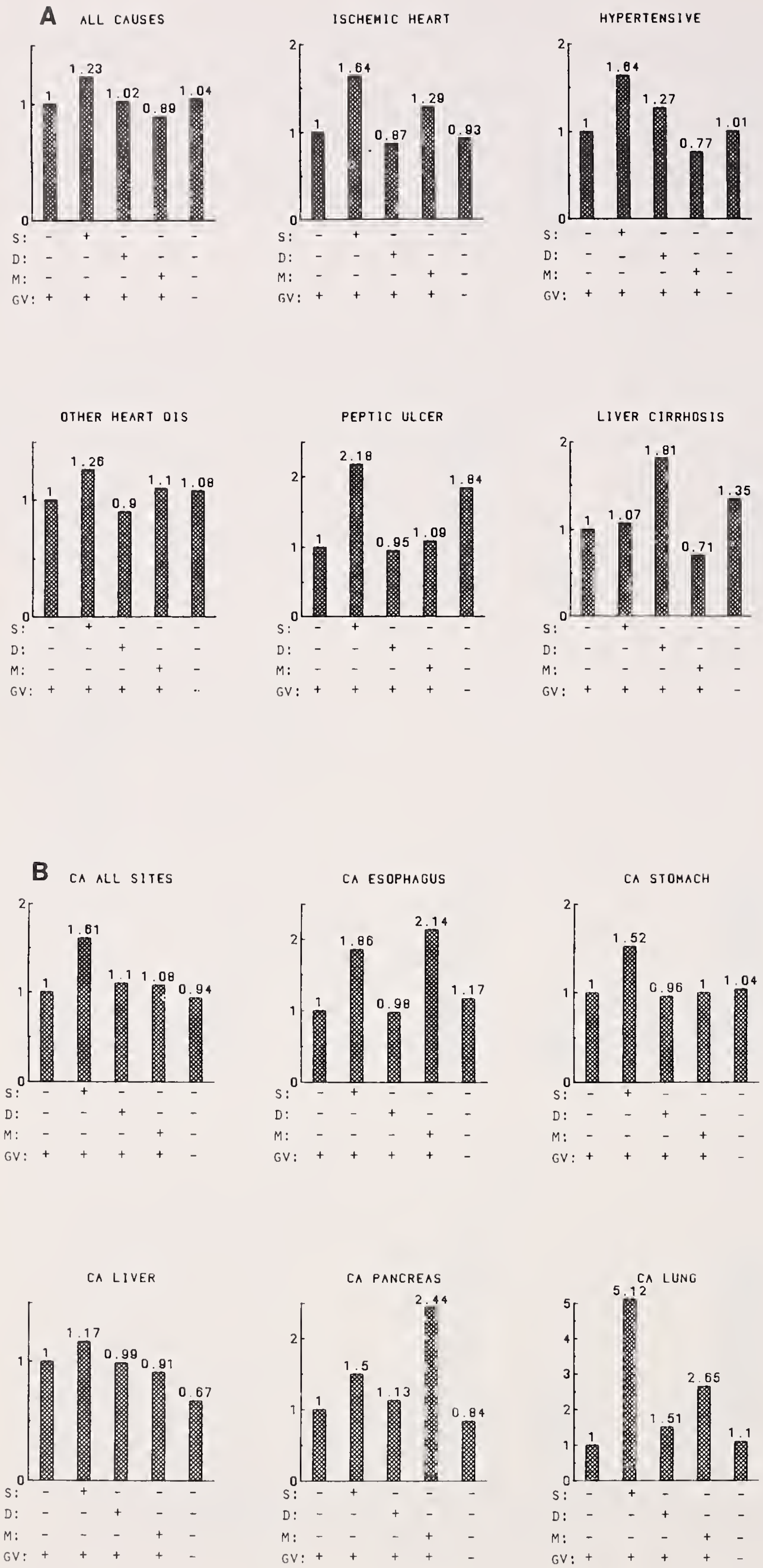


FIGURE 3.—Effect of the addition of 1 factor on SMR for Japanese with SDA-like life-styles for A) selected causes of death and B) cancer of selected sites.

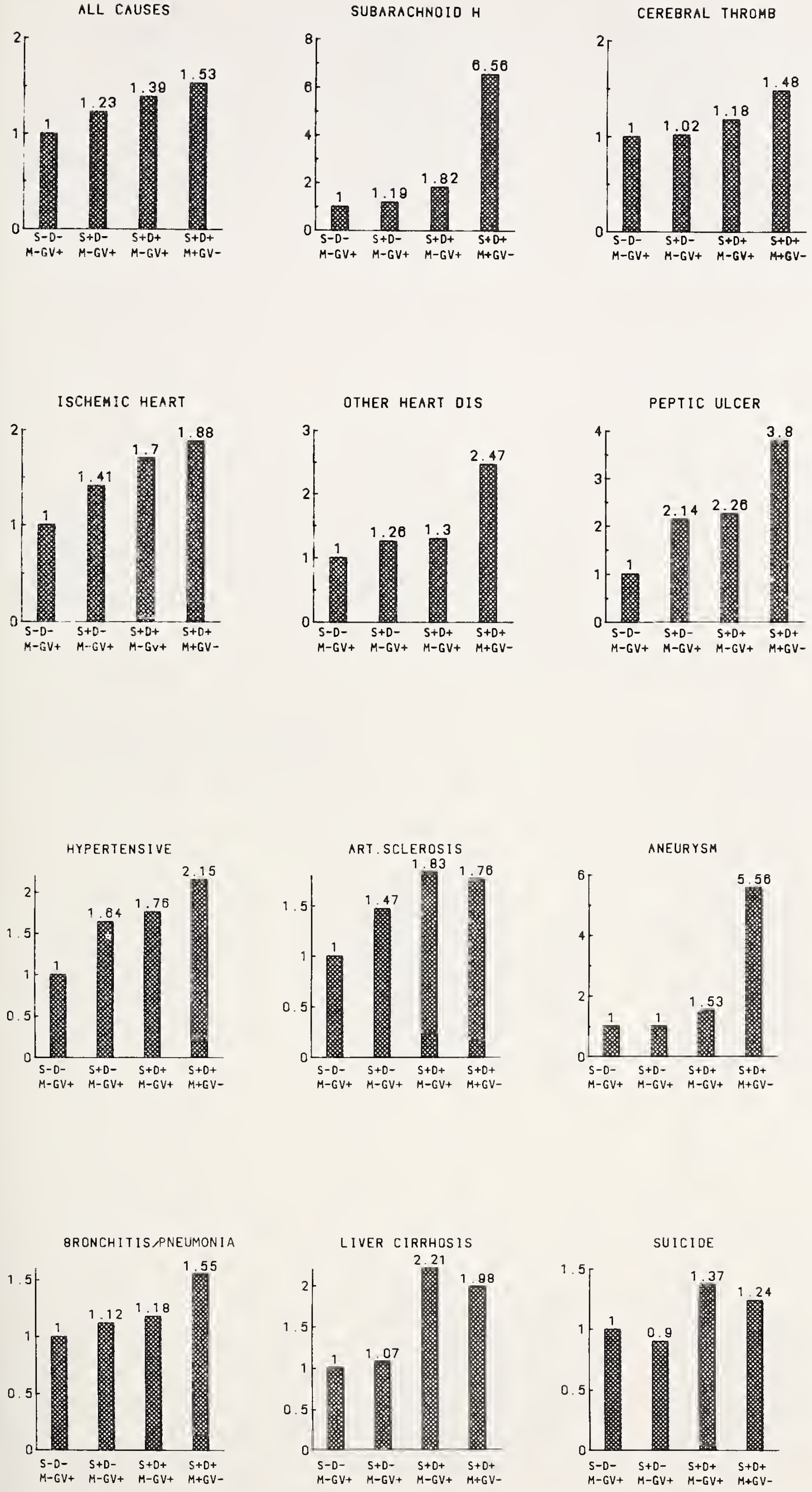


FIGURE 4.—Selected causes of death of Japanese with or without SDA-like life-styles.

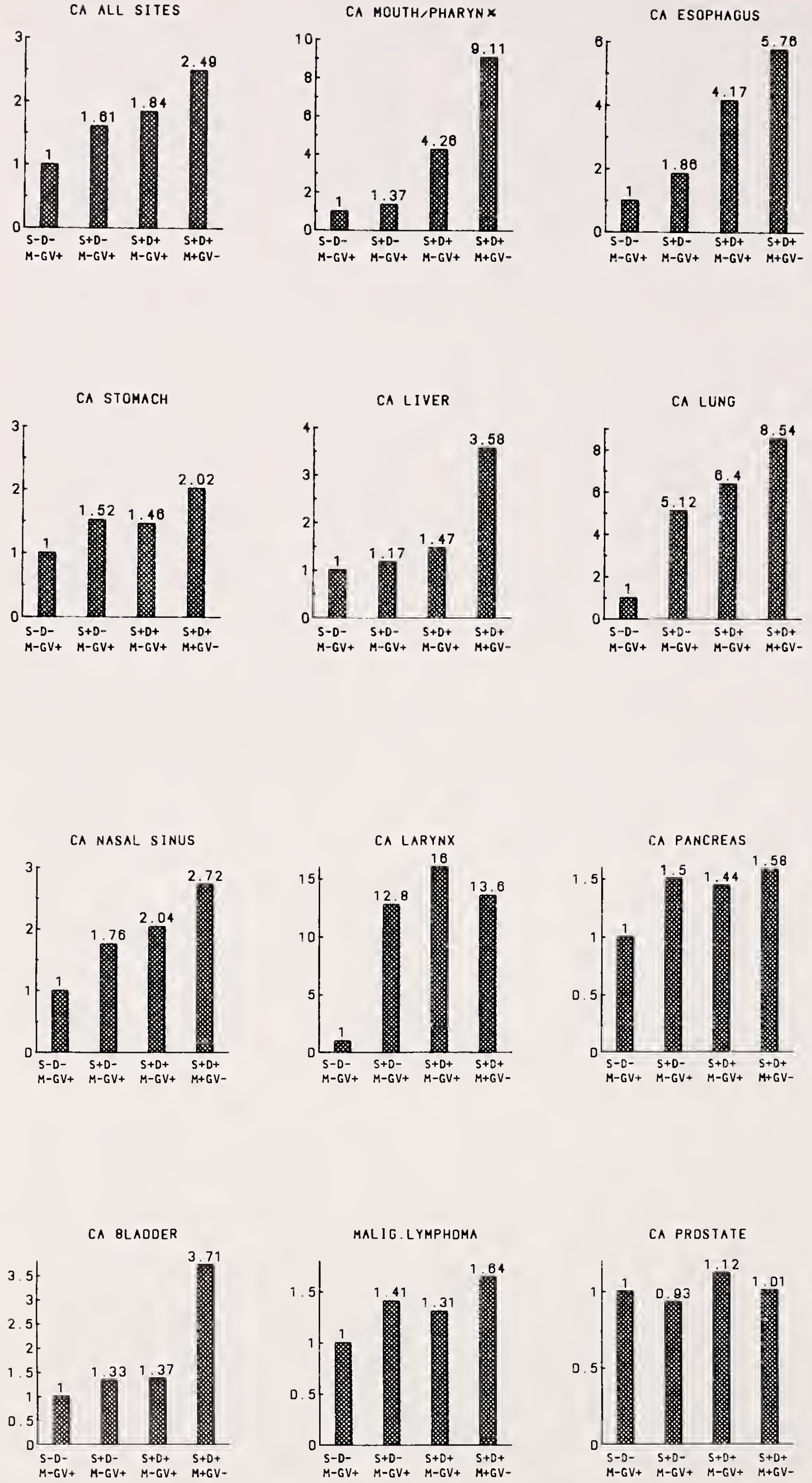


FIGURE 5.—Cancer of selected sites in Japanese with or without SDA-like life-styles.

TABLE 1.—*The RR of Japanese who follow SDA-like life-styles (group 0010) and those who do not (group 1101)*

Cause of death	RR
	Group 0010 to group 1101
Subarachnoid hemorrhage	.153
Cerebrovascular disease	.675
Ischemic heart disease	.532
Other heart disease	.405
Peptic ulcer	.263
Cancer	
All sites	.401
Mouth, pharynx	.110
Esophagus	.174
Stomach	.496
Liver	.279
Lung	.117
All causes of death	.656

diet, the risk of pancreatic cancer rose dramatically. For all other major causes of death, the risk was elevated primarily when daily cigarette smoking was added.

Next, the combined effect of daily cigarette smoking and alcohol consumption was studied. The SMR for Japanese who follow the SDA dietary customs but who smoke cigarettes daily (group 1010) and who both smoke cigarettes and drink alcohol daily (group 1011) mostly range between groups 0010 and 1101 (tables 2, 3; figs. 4, 5). The increase of risk by the addition of cigarette smoking to the SDA-like life-style of group 0010 is clear for all causes of death, ischemic heart disease, peptic ulcer, cancer of all sites, and cancers of the stomach and lung. The balance between groups 1011 and 1101, which probably corresponds to the effect of nutrition, is most striking for subarachnoid hemorrhage, aneurysm of the aorta, other heart diseases, peptic ulcer, and cancers of the mouth, pharynx, stomach, liver, and urinary bladder. A limited influence of nutrition was also seen for cancers of the esophagus and lung.

Modifications of each life-style variable appeared to have different effects on the reduced risk of dying from cancer (tables 2, 3; fig. 6). When people with an SDA-opposite life-style stop smoking cigarettes daily but retain other habits, the risk of most diseases declines: all causes of death to 0.51, cancer of all sites to 0.46, stomach cancer to 0.76, and lung cancer to 0. When people with an SDA-opposite life-style stop drinking alcohol daily, the risk for most diseases also declines: all causes of death to 0.86,

TABLE 2.—*The SMR for selected causes of death for Japanese male nonsmokers and different combinations of life-style variables*[a]

Cause of death	Groups							
	0111	0110	0101	0100	0011	0010	0001	0000
	Observed person-yr[b]							
	5,797	13,068	1,241	2,154	41,745	157,228	13,663	54,617
	No. of deaths							
	98	169	16	30	816	2,738	259	1,006
All causes of death	1,628.8	1,321.1	1,159.1	1,389.8	1,506.6	1,482.4	1,477.6	1,542.2
Cerebrovascular disease	581.0	298.8	578.0	514.8	492.7	469.5	494.1	468.6
Subarachnoid hemorrhage	16.0	8.0	0	0	4.6	9.0	0	8.7
Ischemic heart disease	135.2	102.2	0	0	69.3	79.3	77.6	73.9
Other heart disease	34.4	101.9	141.4	46.5	83.8	93.0	56.3	100.5
Hypertensive heart disease	0	16.0	0	0	26.5	20.8	14.1	21.0
Pneumonia, bronchitis	48.2	16.0	0	0	42.5	65.3	74.0	72.7
Peptic ulcer	16.9	15.0	0	0	13.0	13.7	18.4	25.2
Cirrhosis of the liver	80.2	22.9	0	44.6	58.8	32.4	63.7	43.7
Aneurysm	0	0	0	0	0	3.2	0	0
Suicide	49.0	22.5	0	50.7	30.9	24.8.	27.7	38.2
Cancer								
All sites	450.3	351.5	367.9	470.9	356.7	324.4	347.4	305.9
Mouth and pharynx	0	0	0	0	3.9	2.7	0	1.5
Esophagus	16.0	23.8	0	0	10.9	11.1	14.1	13.0
Stomach	235.7	141.2	217.0	233.8	135.9	141.2	143.2	146.6
Liver	49.0	31.2	0	141.7	33.8	34.1	16.1	22.7
Pancreas	0	39.7	0	0	18.4	16.3	7.4	13.7
Nasal sinus	0	7.5	13.7	0	8.1	2.5	7.4	1.2
Larynx	0	0	0	0	0	0.5	0	0
Lung	16.0	46.4	0	0	26.4	17.5	66.7	19.3
Prostate	64.2	0	0	0	10.6	10.3	11.0	6.6
Bladder	0	0	0	0	9.9	7.6	4.5	3.7
Malignant lymphoma	0	15.0	0	0	14.7	10.7	7.4	6.7

[a] Data are from a prospective study conducted in Japan, 1966–81.

[b] On average, these values represent 13.3 times the actual numbers of men observed.

TABLE 3.—*The SMR for selected causes of death for Japanese male smokers and different combinations of life-style variables*[a]

Causes of death	Groups							
	1111	1110	1101	1100	1011	1010	1001	1000
	Observed person-yr							
	41,157	43,399	11,331	12,407	273,539	493,125	111,213	209,397
	No. of deaths							
	595	596	198	187	5,569	8,536	2,279	3,797
All causes of death	1,833.9	1,644.5	2,261.2	1,937.2	2,064.0	1,830.0	2,121.0	1,901.2
Cerebrovascular disease	482.9	334.8	447.1	458.0	584.4	472.9	574.6	478.9
Subarachnoid hemorrhage	17.3	11.8	59.0	8.2	16.4	10.7	18.8	14.5
Ischemic heart disease	146.1	166.2	149.0	130.3	135.2	130.7	156.1	140.4
Other heart disease	107.9	116.3	229.5	111.5	121.2	117.4	131.4	143.2
Hypertensive heart disease	27.5	16.4	44.7	38.7	36.7	34.1	39.8	34.2
Pneumonia and bronchitis	81.4	74.0	101.3	106.5	77.2	73.3	86.3	75.6
Peptic ulcer	26.0	30.6	52.1	23.0	30.9	29.8	27.8	32.2
Cirrhosis of the liver	69.2	32.4	64.2	22.9	71.5	34.7	75.9	43.8
Aneurysm	2.8	3.7	17.8	17.3	4.9	3.2	3.7	3.5
Suicide	29.8	12.2	30.7	12.7	31.0	22.3	39.3	17.3
Cancer								
All sites	542.0	507.8	808.4	585.6	595.1	522.4	574.5	548.3
Mouth and pharynx	11.2	0	24.6	0	11.5	3.7	7.3	2.4
Esophagus	49.3	14.6	63.9	34.3	46.3	20.7	37.7	16.6
Stomach	168.2	174.1	284.7	142.2	206.4	215.0	219.3	224.3
Liver	57.7	57.2	122.1	66.8	50.1	40.0	58.7	48.8
Pancreas	23.9	37.9	25.7	35.7	23.5	24.4	21.0	24.9
Nasal sinus	4.5	0	6.8	7.1	5.1	4.4	3.6	4.4
Larynx	2.8	2.7	6.8	0	8.0	6.4	7.8	3.4
Lung	106.3	109.4	149.5	132.0	112.0	89.6	113.3	104.0
Prostate	2.4	12.8	10.4	21.0	11.5	9.6	10.1	11.8
Bladder	19.2	12.1	28.2	0	10.4	10.1	11.3	11.0
Malignant lymphoma	15.8	8.3	17.6	16.3	14.0	15.1	10.2	11.3

[a] *See* footnote *a*, table 2.

cancer of all sites to 0.72, esophagus to 0.54, stomach to 0.50, liver to 0.55, and lung to 0.88. When these people stop eating meat daily, their risks for most diseases also go down: all causes of death to 0.94, cancer of all sites to 0.71, stomach to 0.77, and lung to 0.76. Finally, when they start eating green and yellow vegetables daily, risks for most diseases also drop: all causes of death to 0.81, cancer of all sites to 0.67, esophagus to 0.77, stomach to 0.59, liver to 0.47, lung to 0.71, and prostate to 0.23. Figure 2 illustrates that for cancer of all sites and of the lung, smoking cessation was most effective in reducing the risk, whereas for stomach cancer, cessation of daily alcohol consumption had the strongest effect. In both instances, daily intake of green and yellow vegetables ranked second in reducing the risk.

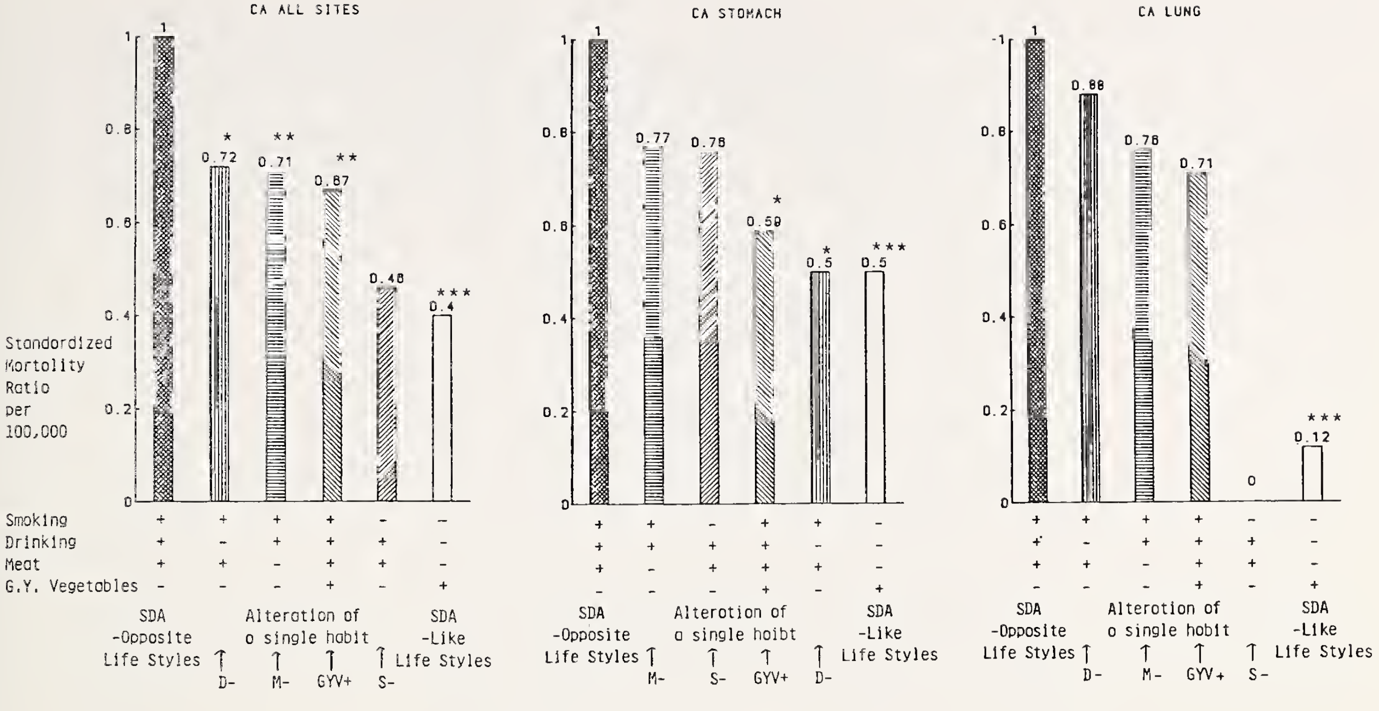
We did a logistic regression analysis on the material with satisfactory "goodness-of-fit" to calculate the RR for various causes of death in Japanese with different combinations of life-style variables. Our results (table 3) clearly indicated that for most diseases, cigarette smoking showed the highest RR and that an interaction or confounding, or both, existed among the variables (e.g., the combined habit of daily smoking and drinking on esophageal cancer risk and daily intake of meat and green and yellow vegetables on colon cancer risk).

DISCUSSION

Phillips and Kuzma (*1*) reported that SDA in Southern California are a low-risk population for developing cancers of many sites. The low risks are generally attributed to life-style practices and dietary habits, including abstinence from smoking, drinking, and meat intake. Most SDA also tend to eat dark green and yellow vegetables more frequently than other populations.

To confirm that such practices lower the risk of major causes of death, particularly cancer, we performed a comparative analysis for different groups of the general population with various life-styles using results of follow-up of an ongoing large-scale cohort study in Japan. These findings clearly indicated that those with an SDA-opposite life-style have significantly elevated mortality for all causes of death, cancers of all sites, and cancers of the mouth and pharynx, esophagus, stomach, liver, and lung compared with the group who follow an SDA-like life-style.

What would happen if SDA would daily smoke ciga-



* significant at 5% level, ** 1% level, *** 0.1% level

FIGURE 6.—Strategies for reducing high cancer risks in Japanese with SDA-opposite life-styles: Effect of alteration of a single habit with other habits retained.

rettes, drink alcohol, eat meat, or stop eating green and yellow vegetables, but retain all other habits? What would happen if daily cigarette smoking and alcohol consumption were added to SDA life-styles? Such issues were studied in persons with SDA-like life-styles except for selected habits (groups 1010, 0011, 0110, and 0000). The results showed that the alteration of a single habit resulted in risk modification for each cause of death. Risks of most diseases tend to rise most distinctly when daily cigarette smoking is added, whereas the addition of alcohol and meat intake appears to elevate the risks for cirrhosis of the liver and pancreatic cancer, respectively, most strikingly.

Furthermore, we observed that the risk for each disease increased again uniquely when daily smoking and drinking are added as variables (group 1011). For some diseases, risk is not elevated even when drinking of alcohol daily is added to daily smoking (e.g., peptic ulcer, bronchitis, cancers of all sites, stomach, larynx, pancreas, and bladder). However, the risk of some diseases is markedly elevated when both habits are combined (e.g., cirrhosis of the liver, cancers of the mouth, pharynx, and esophagus). The remainder of the risk must be attributed to the combined influence of the unique SDA-like dietary patterns. In other words, the risks of some diseases rise significantly when changes in dietary patterns (from eating green and yellow vegetables and no meat daily to no green and yellow vegetables and meat daily) are added to the combined habits of daily smoking and drinking (e.g., subarachnoid hemorrhage, aneurysm of the aorta, cancers of the liver and bladder). Such a pattern of rise in risk according to the life-style change is observed for selected causes of death sharing similar or related pathology or etiology. The pattern of risk elevation according to life-style change is unbelievably similar between subarachnoid hemorrhage and aneurysm of the aorta, between cancer of the liver and of the bladder, and between stomach and peptic ulcer neoplasms.

What would happen if people with an SDA-opposite life-style stop smoking cigarettes, drinking alcohol, or eating meat daily, but start eating green and yellow vegetables daily and keeping all other habits unchanged? These issues were also studied (groups 0101, 1100, 1001, and 1111). The results revealed that the alteration of a single habit resulted in risk modification for each cause of death. Risks of most diseases decline when daily cigarette smoking is excluded. The cessation of daily consumption of alcohol and meat also appeared to lower cancer risk in most instances. Moreover, we observed that the risk for cancer is decreased considerably when subjects start eating green and yellow vegetables daily.

Cessation of daily cigarette smoking was most effective in reducing the risk of cancers of the lung and of all sites. Daily intake of green and yellow vegetables reduced the risk of all these cancers effectively.

We studied the possible interaction of these life-style variables using Cox's logistic model and noted important interactions and confounding which should be borne in mind when investigating the underlying influence of each life-style variable.

Thus by studying the cancer risk among groups with

TABLE 4.—*Logistic regression analysis by maximum likelihood method*[a]

Cause of death	R S	R M	R G	R D	R S×M	R S×G[b]	R S×D	R M×G	R M×D	R G×D
All causes of death	1.277[c]	1.034	0.992	1.032	1.258 (0.953)	1.287 (1.016)	1.413 (1.072)	0.881 (0.859)[d]	1.127 (1.056)	0.994 (0.971)
Cerebrovascular disease	1.020	0.921	0.979	1.049	0.839 (0.893)	1.000 (1.001)	1.199 (1.121)	0.775 (0.860)	1.114 (1.153)	1.082 (1.054)
Subarachnoid hemorrhage	1.867	1.641	1.223	0.476	2.356 (0.769)	1.450 (0.635)	2.624 (0.295)	1.142 (0.569)	1.491 (1.909)	0.604 (1.037)
Ischemic heart disease	1.992[c]	0.941	1.122	1.056	1.846 (0.955)	1.857 (0.831)	2.223 (1.067)	1.423 (1.378)	0.929 (0.935)	1.075 (0.907)
Other heart disease	1.463[d]	1.805	0.987	0.759	1.667 (1.050)	1.226 (0.849)	1.411 (1.271)	0.831 (0.776)	0.925 (1.123)	0.789 (1.053)
Hypertensive heart disease	1,920[e]	0.632	1.212	1.045	1.948 (1.605)	1.843 (0.793)	2.117 (1.055)	0.430 (0.561)	0.766 (1.160)	1.267 (1.000)
Liver cirrhosis	0.990	0.504	0.743	1.487	0.701 (1.405)	0.785 (1.067)	1.718 (1.167)	0.488 (1.304)	0.771 (1.029)	1.320 (1.195)
Cancer										
All sites	1.770[c]	1.455[d]	1.050	1.070	2.143 (0.832)	1.704 (0.917)	1.900 (1.003)	1.169 (0.765)[d]	1.610 (1.034)	1.180 (1.050)
Esophagus	1.453	2.175	0.967	0.990	2.019 (0.639)	1.723 (1.226)	3.186 (2.215)[e]	1.281 (0.609)	2.573 (1.195)	0.999 (1.044)
Stomach	1.522[c]	1.323	0.960	1.045	1.307 (0.649)[e]	1.482 (1.014)	1.522 (0.957)	1.073 (0.845)	1.709 (1.236)	0.945 (0.942)
Colon	1.056	2.378	0.683	0.660	1.464 (0.583)	0.772 (1.070)	0.784 (1.087)	0.357 (0.220)[e]	0.965 (0.615)	0,933 (2.069)[e]
Liver	2.079[d]	2.023	1.474	0.914	3.886 (0.924)	1.750 (0.571)	2.535 (1.334)	1.998 (0.670)	1.842 (0.996)	1.365 (1.013)
Pancreas	2.152[e]	1.408	1.523	0.794	3.067 (1.012)	2.081 (0.635)	1.832 (1.072)	2.385 (1.112)	0.710 (0.635)	1.389 (1.149)
Lung	4.261[c]	1.625	0.732	1.648	5.719 (0.826)	3.752 (1.203)	4.930 (0.702)	1.081 (0.909)	2.156 (0.806)	1.280 (1.061)
Prostate	1.710	2.534	1.212	1.500	2.444 (0.564)	1.384 (0.668)	1.398 (0.545)	2.196 (0.715)	2.824 (0.743)	2.334 (1.284)
Malignant lymphoma	1.673	1.089	1.656	0.980	2.082 (1.143)	2.136 (0.771)	1.431 (0.873)	1.133 (0.628)	1.465 (1.373)	1.819 (1.121)

[a] *See* footnote *a*, table 2. S=smoking; M=meat; G=green and yellow vegetables; and D=drinking.

[b] Examples of calculation: RR of esophageal cancer for those with combined habit of daily smoking and daily drinking: R S×D=R S×R D×R SD=1.453×0.990×2.215=3.186 (*numbers in parentheses*).

[c] *P*=.001

[d] *P*=.01

[e] *P*=.05

differing life-styles, we could evaluate the effect of risk reduction by modifying life-style variables, although we advise that caution must be taken because some of the groups are of limited sample size. Cancer chemoprevention and intervention studies contemplated in many areas in the world (e.g., the United States, Soviet Union, and China) should be carefully planned, with life-style modification strategies suggested by the results of this study kept in mind.

REFERENCE

(*1*) PHILLIPS RL, KUZMA JW: Rationale and methods for an epidemiologic study of cancer among Seventh-Day Adventists. Natl Cancer Inst Monogr 47:107–112, 1977

SESSION IV

Cancer Related to Occupation and Radiation Exposure

Uses of a Cancer Registry in the Assessment of Occupational Cancer Risks [1, 2]

John M. Peters, David H. Garabrant, William E. Wright, Leslie Bernstein, *and* Thomas M. Mack [3]

ABSTRACT—Five approaches for the evaluation of occupational factors in cancer etiology are described. These approaches, based on one's having access to cancer registry data, are for examining cancer profiles for industry and occupation, evaluating information on occupation and industry to infer exposure, observing time trends in incidence to evaluate tumors of occupational interest, using cases of interest to form the basis for case-control studies, and linking cohorts with known exposure to the tumor registry to ascertain cancer incidence in that cohort.—Natl Cancer Inst Monogr 69: 157-161, 1985.

Given the data of a large cancer registry containing information on occupation and industry, what are some of the approaches one can take to investigate the relationship between work and cancer? The 5 approaches we have followed are: 1) examining cancer profiles or patterns for industry or occupation, or both, using PIR; 2) evaluating information on occupation and industry to infer exposure; 3) observing time trends in incidence to evaluate tumors of occupational interest; 4) starting with cases of interest to form the basis for case-control studies evaluating occupational factors, and 5) linking cohorts of individuals with known exposure to the tumor registry to ascertain cancer incidence in that cohort.

PROFILES OR PATTERNS FOR SPECIFIC OCCUPATIONS OR INDUSTRIES

In examining a large data set, such as the Los Angeles County Tumor Registry has, one can note many occupations or industries in which interesting patterns of tumor incidence occur. Of course, because of the many possible comparisons, some of these relationships are spurious. Our information on occupation and industry is coded according to the 1970 Bureau of Census classification. The categories in this system are broad and tend to obscure information on some occupations. However, many leads appear to be based on large numbers of cases or high risks, or both, which should or could be investigated. For example, multiple myeloma is excessive in female cosmetologists (*1*). This excess is not accounted for by race and is particularly interesting in light of potential exposures in beauty shops (table 1). Cosmetologists, beauticians, and manicurists work with many chemical materials, some of which are known to be mutagenic or carcinogenic. This lead is being followed up with a case-control study of cosmetologists. Among the patients who demonstrate impressive excesses are those with lung cancer and multiple myeloma. The controls are cosmetologists who have other tumors that are not excessive in number. The cosmetologists will be interviewed and differences in work patterns and processes will be assessed. Because cancer of the central nervous system in aircraft workers is excessive in Los Angeles County (*2*), we are also conducting a case-control study with this group.

Another example of our examining cancer profiles within occupational categories involves the evaluation of cancer risk in occupations in which exposure to electromagnetic fields is possible. Milham (*3*) noted that persons holding certain jobs involving exposure to electromagnetic fields have excess mortality from leukemia. We examined these same occupational categories and extended the observation to show that not only do these occupational groups (table 2) have excess leukemia incidence, but the excess is accounted for by acute leukemia and, in particular, acute myelogenous leukemia (*4*).

INFERENCE OF EXPOSURE BY USE OF INFORMATION ON OCCUPATION AND INDUSTRY

We have tended to look for occupations in which possible exposures of potential etiologic significance occur, and it has also been our practice to look for tumors in which occupational exposures have plausible etiologic connections. Therefore, we were slow to recognize that the excess of colon cancer among occupations in which no specific exposure could be thought of might have some important implications. Because some of these occupations were sedentary in nature, we asked the question: "Does activity on the job relate to colon cancer incidence?" To answer this question, we classified all occupations into 3 categories of activity: sedentary, moderately active, and active. We (*5*) then looked at colon cancer incidence primarily using the PIR and found that people with sedentary occupations had an approximately 60% excess of colon cancer (table 3). Inasmuch as differences are known in colon cancer incidence by socioeconomic status, race, ethnicity, country of origin, etc., we examined these factors to see if they

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ABBREVIATIONS: PIR = proportional incidence ratio(s); AAIR = age-adjusted incidence rates.

[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16-20, 1984.

[2] Supported in part by Public Health Service grant CA34958 from the National Cancer Institute, American Cancer Society grant SIG-2, and contract No. R01-OH0413 with the National Institute for Occupational Safety and Health.

[3] Department of Preventive Medicine, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033.

TABLE 1.—*Substances frequently used by cosmetologists*

Products	Chemical components
Shampoos	Sodium lauryl sulfate, propylene glycol, methyl cellulose, formaldehyde, lecithin, various dyes
Dyes	2,4-Diaminoanisole, 2,4-diaminotoluene, *n*-nitro-*o*-phenylenediamine, 4-ethoxy-*m*-phenylenediamine, hydrogen peroxide
Conditioners	Stearalkonium chloride, glycerolstearate alcohols (benzyl alcohols, 1-hexadecanol), various dyes
Permanent wave solution	Ammonium thioglycolate, alkaline sulfite
Polish remover	Acetone, ethylacetate
Nail polish	Toluene, butyl acetate, nitrocellulose, various dyes
Cosmetics	Magnesium aluminum silicate, titanium dioxide, talc, mica, various dyes
Hair spray	Isobutane, methylene chloride, propane vinyl acetate, vinyl neodeconate, crotonic acid
Artificial nails	Ethyl methacrylate, *o*-toluidine, benzoyl peroxide

TABLE 2.—*Leukemia incidence in men occupationally exposed to electrical and magnetic fields: Los Angeles County, white males, 1972–79*

Occupation	No. of cases of: All leukemia		Acute leukemia		Acute myelogenous leukemia	
	No.	PIR	No.	PIR	No.	PIR
Electronic technicians	4	95.6	3	143.5	3	178.6
Telegraph operators	0		0		0	
Electricians	12	136.8	6	146.4	5	151.1
Linemen, power	2	317.3	2	593.6	2	816.6
Television and radio repair	1	123	0		0	
Power station operators	1	281.1	1	460.1	1	685.4
Motion picture projectionists	1	230.7	1	471.8	1	564
Welders and flame cutters	6	96.2	4	133.9	4	171.2
Electrical engineers	6	131.6	4	177.8	4	215.5
Conductors and motormen, urban rail transit	0		0		0	
Linemen, telephone	2	309.2	2	567.6	2	768.8
All of above jobs	35	128.6	23	172.6	22	207.1

explained the relationship between job activity and colon cancer incidence. Table 4 presents colon cancer incidence categorized by activity and socioeconomic status. The general trend persists that people holding sedentary jobs, despite socioeconomic status, have an excess risk of colon cancer. A similar tabulation according to race that shows persistence of the relationship of sedentary jobs to colon cancer risk across categories of race is given in table 5.

Because carcinogens in the colon may somehow be responsible for the risk and the carcinogenic concentration may increase from the proximal to distal colon, we examined the cancer risk by location within the colon (table 6). Generally, the risk increases from the proximal to distal colon, supporting the hypothesis presented. This finding has two important implications: 1) Exercise might decrease

TABLE 3.—*The AAIR/100,000 and PIR by occupational activity level for selected cancer sites among males of all races aged 20–64 yr, diagnosed between 1972 and 1981 in Los Angeles County*

Cancer site	Occupational activity level: Sedentary	Moderate	High	Total	Risk ratio: Sedentary:high	95% Confidence limits	
	No. of patients classified						
Colon	326	2,352	272	2,950			
Rectum[a]	104	955	154	1,213			
All nonbowel	2,999	24,923	3,802	31,724			
	AAIR/100,000[b]						
Colon[c]	24.6	21.6	13.4	20.8	1.8	1.6,	2.2
Rectum[a]	8.1	9.1	7.9	8.9	1.0	0.8,	1.3
All nonbowel	221.3	231.6	190.1	226.1	1.2	1.1,	1.2
	PIR						
Colon[c]	122	101	78	100	1.6	1.3,	1.8
Rectum[a]	95	100	108	100	0.9	0.7,	1.1
All nonbowel	101	99	102	100	1.0	0.9,	1.0

[a] Rectosigmoid was excluded.

[b] Values were adjusted uniformly within site for patients whose occupations were unreported.

[c] Trend is statistically significant; one-sided $P<.0001$.

TABLE 4.—*The PIR for colon cancer by occupational activity level by social class among non-Hispanic white males aged 20–64 yr diagnosed between 1972 and 1981 in Los Angeles County*[a]

Social class	AAIR/100,000	No. of patients classified	PIR by activity				Risk ratio, sedentary: high
			Sedentary	Moderate	High	Total	
1 (high)	24.0	304	116	99	71	100	1.6
2	22.2	743	119	102	65	100	1.8
3	20.3	590	140	99	80	100	1.8
4	17.8	646	99	104	82	100	1.2
5 (low)	18.0	84	112	106	62	100	1.8

[a] Six of unknown social class were excluded.

TABLE 5.—*The PIR for colon cancer by occupational activity level and race/nativity among males aged 20–64 yr diagnosed between 1972 and 1981 in Los Angeles County*

Nativity/race	AAIR/100,000	No. of patients classified	PIR by activity				Risk ratio of sedentary: high
			Sedentary	Moderate	High	Total	
Blacks	21.9	253	143	100	85	100	1.7
North American Hispanic whites	18.2[a]	108	151	97	101	100	1.5
Immigrant Hispanic whites	11.0[a]	46	107	106	70	100	1.5
Non-Hispanic whites	21.1	2,373	122	101	75	100	1.6

[a] Value was adjusted for patients in hospitals that did not provide birthplace.

the incidence of colon cancer, and 2) activity levels must be considered in studies of colon cancer etiology because activity appears to be at least as large a risk factor as any dietary component studied. This study is discussed more fully elsewhere (*5*).

Another example of how one can use occupations to infer exposure relates to dust. We classified all the occupations according to probability of exposure to dust and type of dust. This was done because workers in certain occupations that involve considerable exposure to dust, such as coal mining and asbestos work, have been reported to have an excess of stomach cancer. Our preliminary results so far indicate that their risk for stomach cancer is elevated, which would fit into the stomach cancer hypothesis presented in another paper in this conference.

A third example of how we classified occupations to represent exposure is that of examining jobs in which exposure to gasoline occurs. We observed an increased incidence of leukemia that could be related to the benzene in gasoline.

TABLE 6.—*The PIR for colon and rectal cancer by occupational activity level and anatomic subsite among males of all races aged 20–64 yr diagnosed between 1972 and 1981 in Los Angeles County*

Subsite	AAIR/100,000	No. of patients classified	PIR by activity				Risk ratios	
			Sedentary	Moderate	High	Total	Ratio of sedentary: high	95% Confidence limits
Cecum	3.6	509	108	102	83	100	1.3	0.9, 1.9
Ascending colon	2.0	290	126	95	118	100	1.1	0.7, 1.6
Hepatic flexure	0.6	90	120	100	86	100	1.4	0.6, 3.4
Transverse colon[a]	1.9	259	138	101	70	100	2.0	1.1, 3.3
Splenic flexure	0.8	110	129	102	62	100	2.1	0.8, 4.9
Descending colon[b]	1.8	255	154	101	57	100	2.7	1.5, 4.8
Sigmoid colon[c]	8.6	1,192	123	101	78	100	1.5	1.2, 2.0
Rectosigmoid colon	3.1	435	94	102	97	100	1.0	0.6, 1.4
Rectum	8.9	1,213	95	100	108	100	0.9	0.7, 1.1
Colon, multiple or unknown	1.2	164	101	104	72	100	1.4	

[a] Trend in PIR is statistically significant; one-sided $P = .02$.

[b] Trend in PIR is statistically significant; one-sided $P = .0008$.

[c] Trend in PIR is statistically significant; one-sided $P = .002$.

TIME TRENDS IN INCIDENCE OF TUMORS OF OCCUPATIONAL INTEREST

Patients with pleural and peritoneal malignant mesothelioma who were diagnosed from 1972 to 1979 were studied. Occupational histories were obtained during interviews, and histopathology of the tumors was reviewed and classified by a member of a Mesothelioma Reference Panel, who was unaware of the patients' exposure histories. About one-half of the patients whose cases were reviewed had likely exposure to asbestos at work. The greatest proportion of patients who were designated as having malignant mesothelioma by our pathologist were those who were likely to have had the heaviest asbestos exposures. Although the number of cases reported to our tumor registry increased between 1972 and 1979, no upward trend of incidence over time was apparent among those designated as malignant mesothelioma.

The AAIR for malignant mesothelioma were lower than in other studies. The well-recognized interobserver variability in the diagnosing of malignant mesothelioma apparently produces elevated estimates of incidence and overestimation of trends of incidence. The interobserver variability may result from different physicians' awareness of malignant mesothelioma occurrence, a lack of precise histopathologic criteria for the diagnosis, or the influence of a history of asbestos exposure on the interpretation. We concluded that a history of asbestos exposure may bias interpretation of histopathology and the exposure history should not be used to make the histologic diagnosis. This study is described more fully elsewhere (*6*). This approach demonstrates the value of including pathologists in the evaluation of tumor registry data.

TUMOR REGISTRY CASES FORMING THE BASIS FOR CASE-CONTROL STUDIES

We noted that chemists whose records were on file in the tumor registry had an excess of malignant melanoma. We therefore interviewed chemists living in Los Angeles County so we could generate hypotheses that might explain their apparent excess of this tumor. Interviews that included information on work history and exposure to specific chemicals were conducted by telephone. Chemists with melanoma were found to be better educated than chemists with other cancers, and they reported to have worked more with organic chemicals. They also cited more exposure to multiple chemicals, solvents, plastics, pesticides, benzoyl peroxide, and ionizing radiation (*7*). Although differences in educational level may account for the differences in exposure reported by patients and controls, the hypotheses that specific chemical exposures are related to melanoma occurrence are plausible and deserve further study. We also suggest that this method of generating hypotheses about cancer cases using those identified from registries could be used more extensively (*7*).

Another example of how cases from a tumor registry can be evaluated for occupational factors involves a study of childhood brain tumors (*8*). Ninety-two children with brain tumors and who were less than 10 years old were compared with 92 matched controls for parental occupational history. Mothers of patients were more likely to have held occupations involving chemical exposure than those of controls, and fathers of patients had occupations involving solvents or employment in the aircraft industry (table 7). These 3 factors were not affected by adjustment for the potential confounding variables, such as diet, smoking habits, and alcohol use, examined in the study.

In an attempt to gain more specific information on exposures within the aircraft industry, we interviewed the fathers in this study to obtain complete occupational histories. The occupational histories of the fathers of children with tumors of the central nervous system and controls who worked in the aircraft industry were compared. We observed a high frequency of exposure to solvents by the fathers of the children with tumors of the central nervous system (table 8); exposures to commonly used solvents such as trichloroethylene, methyl-ethyl ketone, and freon are associated with an excess risk for children of fathers employed in the aircraft industry. These data support the idea that solvents are potentially important in the etiology of childhood brain tumors. Whether these exposures produce their effect by causing 1) transmissible genetic changes, or 2) exposure to the pregnant mother, or 3) exposure to the young child is not known.

TABLE 7.—*Matched-pair comparison of parental occupational exposure of cases and controls*[a]

Factor	Concordant pairs: both exposed	Discordant pairs: Cases exposed	Discordant pairs: Controls exposed	Relative risk	One-sided test, *P*
Mother					
Skin contact with chemicals	0	10	3	3.3	.05
Inhalation of chemicals or fumes	1	12	4	3.0	.04
One or both of the above	1	14	5	2.8	.03
Father					
Exposure to chemical solvents	3	17	6	2.8	.02
Exposure to paints	0	7	1	7.0	.04
Employment in aircraft industry	2	10	0	∞	.001

[a] The mother was considered to have been exposed if exposed at any time from 1 yr before conception through lactation. The father was considered to have been exposed if exposed during that period or at the time of diagnosis.

TABLE 8.—*Exposure of fathers of children with brain tumors to solvents*[a]

Exposure to:	Patients	Controls	Odds ratio
Solvents at any time	12	7	∞
Solvents daily	11	6	7.3
Carbon tetrachloride	3	1	3.0
Trichloroethylene	5	0	∞
Methylethyl ketone	7	1	12.6
Toluene	2	0	∞
Freon	4	0	∞
Paints	3	1	3.0
Petroleum products	10	6	3.0
Asbestos/fiberglass	4	3	1.1

[a] No. of fathers of patients and controls = 12 and 10, respectively.

LINKING OF OCCUPATIONAL COHORTS TO TUMOR REGISTRIES

Another important use scientists can make of tumor registries in the study of occupational factors in cancer has to do with record linkage of cohorts of exposed individuals. Groups of persons representing companies, unions, crafts, and others who had identifiable exposure can be examined for cancer incidence in this way. We hope to do this in the future.

SUMMARY

Five approaches by which one can examine occupational factors in cancer etiology have been described; examples have been provided for 4. These approaches have yielded some useful results and many leads. Other persons with access to similar data accumulated in tumor registries may wish to try these and other approaches.

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Cancer Mortality Experience of Woodworkers, Loggers, Fishermen, Farmers, and Miners in British Columbia [1, 2]

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ABSTRACT—To evaluate occupational cancer mortality in British Columbia, we calculated the age-standardized proportional mortality ratios (PMR) and proportional cancer mortality ratios (PCMR) for 4,091 woodworkers, 5,457 loggers, 2,020 fishermen, 4,066 farmers, and 1,912 miners. Woodworkers 20–65 years old had significantly elevated risks of death from stomach cancer (PCMR = 128, *P* <.01) and non-Hodgkin's lymphoma (PCMR = 140, *P* <.05). Loggers appear to have an elevated risk of death from nasal sinus tumors (PCMR = 364, *P* <.05). Fishermen had an elevated risk of stomach cancer (PCMR = 168, *P* <.01). Farmers in British Columbia appeared to have excess risks of stomach (PCMR = 136, *P* <.01) and liver cancer (PCMR = 173, *P* <.05), but decreased risk from lung cancer (PCMR = 76, *P* <.01). Miners had an elevated risk of death from lung cancer (PCMR = 127, *P* <.05) and primary eye tumors (PCMR = 569, *P* <.05).—Natl Cancer Inst Monogr 69: 163–167, 1985.

Researchers in British Columbia have done relatively few studies to investigate job-related cancer. In an attempt to delineate risks for occupational groups in the Province, we analyzed mortality data collected over the period 1950–78. This report presents an overview of male cancer risks for woodworkers, miners, farmers, and fishermen. These 4 groups were selected for presentation because they represent the most economically important occupational groups in the Province.

MATERIALS AND METHODS

Data on 457,083 deaths occurring in the Province from 1950 to 1978 were obtained from the British Columbia DVS. The age group of 20–65 years was selected as the limit for the present analysis, and after all deaths occurring beyond these ages were eliminated, as well as a small number or records with invalid cause of death, sex, or occupational codes, data on a total of 90,726 male deaths were available, including those of 4,091 woodworkers, 5,457 loggers, 4,066 farmers, 2,020 fishermen, and 1,912 miners. Of the 45,967 females who died, only 53 were classified as being employed in these 5 industries, and they were excluded from this analysis.

Cause of death information, as recorded by the attending physician at death, was coded by DVS nosologists according to the Sixth, Seventh, and Eighth Revisions of the International Classification of Diseases over the 29-year period (*1–3*). We reconciled the codes to the format of the Seventh Revision. Occupational information is recorded on each death registration and represents the usual occupation of the decedent. Two occupational coding schemes were used by the DVS from 1950 to 1978, and we reconciled the earlier code to the later 1961 Canadian occupational manual (*4*).

We calculated age-standardized PMR by the method of Monson (*5*) for the 20- to 65-year old males who died; the significance of the PMR was assessed by comparison with the Poisson distribution (*6*). Because significantly elevated or lowered PMR for major causes of death, such as degenerative heart disease, tend to affect individual cancer site PMR values, age-standardized PCMR were calculated by occupational group for all cancer sites. For the entire occupational study, 216 occupations were analyzed according to 158 causes of death.

RESULTS

The woodworkers group (table 1) is composed of carpenters, cabinet and furniture makers, lumber graders and scalers, sawyers in sawmills, and woodworkers not classified elsewhere. Because of their different pattern of mortality, loggers are tabulated separately. The woodworkers demonstrated an elevated risk of death from all cancers combined (PMR = 112, *P* <.01). Other major causes of death consisting of degenerative heart disease (PMR = 96, NS), cerebrovascular accident (PMR = 104, NS), and all accidents (PMR = 103, NS) were within expected limits. Table 2 shows elevated risks of death from stomach cancer in woodworkers (PCMR = 128, *P* <.01) and non-Hodgkin's lymphoma (PCMR = 139, *P* <.05). No nasal sinus tumor deaths were found in the woodworkers group.

Loggers (table 1) demonstrated lowered PMR values for several of the major causes of death including degenerative heart disease (73, *P* <.01) cerebrovascular accidents (72, *P* <.01), and all cancers combined (69, *P* <.01). These lower values appear to be due to the high risk of death

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ABBREVIATIONS: DVS=Division of Vital Statistics; PMR=proportional mortality ratio(s); PCMR=proportional cancer mortality ratio(s); NS=not significant; ICD-7=International Classification of Diseases, Seventh Revision; CI=confidence interval.

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TABLE 1.—*Major causes of death of woodworkers, loggers, miners, farmers, and fishermen, age 20–65 yr, British Columbia 1950–78*[a]

Worker group	Arteriosclerosis and degenerative heart disease (ICD=420–422)			Malignant neoplasms (ICD=140–205, 294)			Cerebrovascular accident (ICD=330–334)			All accidents (ICD=E800–E936)			No. of deaths, all causes
	No.	PMR	95% CI	No.	PMR	95% CI	No.	PMR	95% CI	No.	PMR	95% CI	
Woodworkers	1,211	96	90, 102	877	112[b]	104, 120	191	104	89, 120	745	103	95, 111	4,091
Loggers	969	73[b]	68, 79	608	69[b]	64, 76	143	72[b]	60, 85	2,357	157[b]	151, 164	5,457
Miners	407	75[b]	68, 83	293	85[b]	76, 96	62	77[c]	60, 99	542	132[b]	121, 145	1,912
Farmers	1,339	96	90, 102	857	102	95, 109	225	109	95, 124	492	94	86, 103	4,066
Fishermen	532	91[c]	83, 99	308	84[b]	74, 94	79	92	73, 115	539	130[b]	119, 142	2,020

[a] ICD=International Classification of Diseases (code number).

[b] $P<.01$.

[c] $P<.05$.

from accidents (PMR = 157, $P<.01$). Loggers (table 3) displayed elevated PCMR for nasal sinus cancer (364, $P<.05$), although the number of deaths was small. Stomach cancer was also slightly higher than expected (PCMR = 121), although not significantly so. Values for other tumor sites were within expected limits.

The overall pattern of mortality for fishermen (table 1) indicated slightly lowered mortality for degenerative heart disease (PMR = 91, $P<.05$) and all malignant neoplasms combined (PMR = 84, $P<.01$), with the rate for cerebrovascular accidents as expected (PMR = 92, NS), and all accidents were more common than we anticipated (PMR = 130, $P<.01$). Stomach cancer was significantly elevated (PCMR = 168, $P<.01$), as shown in table 4. In addition, nasal sinus cancer appeared to be elevated although not significantly so (PCMR = 470). Several major sites including colon (PCMR = 84, NS) and lung (PCMR = 84, NS) appeared relatively low.

Farmers demonstrated neither elevated nor lowered risks of death for the major causes of death (table 1). When individual cancer sites were examined (table 5), the farmers showed higher than expected risks for death from cancers of the stomach (PCMR = 136, $P<.01$) and liver (PCMR = 173, $P<.05$). Leukemia mortality also appeared to be elevated (PCMR = 131) although not significantly so. Other major tumor sites displayed PCMR within expected limits, with the exception of lung cancer which was significantly reduced (PCMR = 76, $P<.01$).

Miners showed lower risks of death (table 1) from degenerative heart disease (PMR = 75, $P<.01$), all cancers combined (PMR = 85, $P<.01$), and cerebrovascular accidents (PMR = 77, $P<.05$), but significantly higher risk of accidental death (PMR = 132, $P<.01$). Similarly, deaths from silico-tuberculosis (32 deaths; PMR = 2,438, $P<.01$) and occupational lung disease (69 deaths; PMR = 2,377, $P<.01$) were substantially higher than expected in miners in this Province. The PCMR for lung cancer (PCMR = 127, $P<.05$) and cancer of the eye (PCMR = 569, $P<.05$) were high, although the number of persons who died from the latter tumor were small (table 6). Our analysis also revealed a lower than expected value for cancers of the brain and nervous system (PCMR = 20, $P<.01$); again this was based on small numbers.

DISCUSSION

Occupational studies based on death certificate information are subject to a number of shortcomings, including inaccuracy of cause of death data (*7, 8*) and occupational information (*9*). In addition, use of the PMR does not allow assessment of the overall force of mortality within single occupational groups (*10*) because markedly high or low PMR for a common cause of death may have the effect of lowering or raising PMR for less common causes of death. On the other hand, the PMR has the advantage

TABLE 2.—*The PCMR for selected sites, woodworkers aged 20–65 yr, British Columbia, 1950–78*

ICD-7	Site/type of cancer	No. of deaths	PCMR	95% CI
151	Stomach	116	128[a]	106, 154
153	Colon	54	84	64, 111
157	Pancreas	49	88	66, 116
160	Nasal sinus	0	—	—
162.0, 162.1, 162.8, 163	Lung	283	106	94, 120
200, 202	Non-Hodgkin's lymphoma	42	139[b]	102, 188
204	Leukemia	32	85	60, 121
140–205	All	877	100	—

[a] $P<.01$.

[b] $P<.05$.

TABLE 3.—*The PCMR for selected sites, loggers aged 20–65 yr, British Columbia, 1950–78*

ICD-7	Site/type of cancer	No. of deaths	PCMR	95% CI
151	Stomach	75	121	96, 152
153	Colon	43	97	71, 131
157	Pancreas	29	75	50, 109
160	Nasal sinus	5	364[a]	118, 851
162.0, 162.1, 162.8	Lung	163	90	76, 105
200, 202	Non-Hodgkin's lymphoma	19	89	53, 140
204	Leukemia	31	120	84, 170
140–205	All	608	100	—

[a] $P<.05$.

TABLE 4.—*The PCMR for fishermen aged 20–65 yr, British Columbia, 1950–78*

ICD-7	Site/type of cancer	No. of deaths	PCMR	95% CI
151	Stomach	54	168[a]	129, 220
153	Colon	19	84	50, 132
157	Pancreas	18	90	53, 143
160	Nasal sinus	3	470	96, 1,374
162.0, 162.1, 162.8, 163	Lung	80	84	67, 105
200, 202	Non-Hodgkin's lymphoma	5	49	15, 115
204	Leukemia	12	97	50, 170
140–205	All	308	—	—

[a] $P<.01$.

TABLE 5.—*The PCMR for selected sites, farmers aged 20–65 yr, British Columbia, 1950–78*

ICD-7	Site/type of cancer	No. of deaths	PCMR	95% CI
151	Stomach	124	136[a]	114, 163
153	Colon	60	95	73, 123
155.0	Liver	22	173[b]	108, 262
157	Pancreas	68	121	95, 154
160	Nasal sinus	1	57	1, 319
162.0, 162.1, 162.8, 163	Lung	202	76[a]	65, 87
200, 202	Non-Hodgkin's lymphoma	25	93	59, 137
204	Leukemia	43	131	97, 177
140–205	All	857	100	—

[a] $P<.01$.
[b] $P<.05$.

TABLE 6.—*The PCMR for selected sites, miners aged 20–65 yr, British Columbia, 1950–78*

ICD-7	Site/type of cancer	No. of deaths	PCMR	95% CI
151	Stomach	29	100	66, 144
153	Colon	17	83	48, 133
157	Pancreas	20	112	68, 173
162.0, 162.1, 162.8, 163	Lung	108	127[a]	105, 154
192	Eye	3	569[a]	117, 1,664
193	Brain and nervous system	3	20[b]	4, 59
200, 202	Non-Hodgkin's lymphoma	10	104	49, 191
204	Leukemia	7	59	23, 122
140–205	All	280	100	—

[a] $P<.05$.
[b] $P<.01$.

of avoiding the "healthy worker effect," demonstrated when one is comparing mortality rates for individual occupations with that of the general population (*5*). Furthermore, PMR studies function effectively as screening studies; they are quick, inexpensive, and easy to conduct and have been responsible for elucidating a number of occupational risks (*10–12*). Caution must be used in interpretation of the results, however, inasmuch as computation of large numbers of summary statistics and the testing of their significance may cause spurious disease–occupation associations to appear strictly by chance.

Even with the limitations imposed by the PMR methodology, several findings have appeared in the major industrial groups in the Province. The stomach cancer risk seen in woodworkers in British Columbia may be partly due to socioeconomic factors because several studies have demonstrated an increased risk of this tumor in males of lower socioeconomic status (*13, 14*). Despite the possibility of confounding, there is evidence that the association of stomach cancer and woodworking may be real. The elevated risk among woodworkers in our study confirms observations in the U.S. (*15, 16*), although no corresponding increase has been seen for stomach cancer in British or European woodworkers (*12, 16, 17*). Because the woods processed in this Province and the U.S. Pacific Northwest, i.e., cedar, hemlock, balsam, and fir, are different from the hardwoods such as oak and beech processed in the United Kingdom, further work on dust particle size and the chemistry of the wood itself may help to account for the stomach cancer risk.

Our woodworkers demonstrated an elevated risk for non-Hodgkin's lymphoma, although the excess of Hodgkin's disease reported by Petersen and Milham (*9*) did not appear. In view of the excess of histiocytic lymphomas found in Swedish woodworkers exposed to chlorophenol wood preservatives (*18, 19*), further study of the woodworkers in British Columbia is required.

Loggers had an elevated PCMR for nasal sinus cancer, although no excess was found in other woodworkers. Our findings confirm those of a prior case-control study, which showed an elevated risk for the tumor in forestry workers (*20*).

The increased risk of stomach cancer detected in fishermen may be due to ethnic status confounding. Although the Japanese population of British Columbia is small, they tend to engage disproportionately in commercial fishing. Japanese living here are known to have an elevated risk of death from stomach cancer (*21*). The analysis also demonstrated an increased risk of death from nasal sinus cancer, the incidence of which also appears to be higher in Japanese than in white populations (*22*), although no data are available for the Japanese in British Columbia.

The most important elevated cancer risk among farmers is stomach cancer. Our finding is of special interest because similar risks were reported by Burmeister (*23*) in Iowa farmers and by Milham (*10*) for dairy and poultry farmers in Washington State.

Several investigators (*24–26*) have provided evidence that high nitrate levels in food and drinking water may be associated with an increased incidence of gastric cancer. However in preliminary results of a recent British study, salivary nitrates and nitrites were found to be higher in individuals from areas of low risk of gastric cancer than in those from higher risk areas (*27*). This was thought to be due to higher consumption of nitrate-containing fresh vegetables in the low-risk area, an area of high socioeconomic status. Because several other studies (*28–31*) have shown ambiguous results, more research is needed if we are to determine the significance of levels of nitrate and nitrite concentration in food, drinking water, and body fluids. Correa et al. (*32*) have hypothesized that gastric atrophy and intestinal metaplasia in susceptible individuals may predispose to growth of a bacterial flora which converts nitrates to nitrites and promotes formation of carcinogenic N-nitroso compounds. In view of the intensive use of nitrate-containing fertilizers by North American farmers, rates of gastric atrophy, intestinal metaplasia, and achlorhydria in this occupational group should be investigated.

Farmers in British Columbia who died at 20–65 years of age had an apparent elevated risk of death from primary liver cancer. Due to the possibility of secondary or metastatic liver cancers being incorrectly coded as primary tumors, this finding must be treated with caution (*33*). Further work is needed in the exploration of this association; in a study of Washington State farmers, Milham (*10*) detected an elevated but not statistically significant risk of death from liver cancer, and Stemhagen et al. (*33*) showed an association between primary liver cancer and agriculture.

Lung cancer in farmers is less common than expected. Farmers in this Canadian Province also had a lower risk of death from bronchitis and emphysema (57 deaths; PMR = 74, $P < .05$). These findings are consistent with the low percentages of cigarette smokers found in several detailed health studies of North American farmers (*34, 35*).

Mineral production in British Columbia is mainly copper, lead, zinc, gold, and silver. In addition, molybdenum is also mined in some quantity. Although we now have no uranium industry in the Province, uranium is mined in Saskatchewan and Ontario, and, because miners move frequently, our death certificate study could include some uranium miners. Miners in British Columbia exhibit a higher than expected PCMR for lung cancer. This excess is consistent with high risks for lung cancer found in gold miners (*36, 37*) and uranium miners (*38*). However, an Australian study of gold miners attributed most of the elevated lung cancer to smoking (*39*). There is minimal evidence that exposure to silica may predispose to lung cancer (*40*), although our miners have an elevated risk of death from occupational lung diseases, most of which are diagnosed as silicosis. Unfortunately, no data available on our death registrations separate the different types of mining in which the decedents were employed.

Our finding of a high PCMR for cancer of the eye in miners should be treated with caution as it is based on only 3 deaths. Likewise, the substantially reduced risk for cancers of the brain and nervous system must be investigated in more detail because the numbers of expected deaths were relatively small.

We are currently following up the results from this report with a more detailed study of work history in newly diagnosed male cancer patients. This may enable us to specify more clearly some of the etiologic factors in the workplace related to cancer excesses found in workers in British Columbia.

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Relationship of Occupation With Cancer of the Maxillary Sinuses in Hokkaido, Japan [1, 2]

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ABSTRACT—The age-standardized mortality rates for cancers of the nose, middle ear, and maxillary sinuses in Japan were calculated for 1970 and compared with those for 1975 and 1980. Japan shows a downward trend of these rates in both sexes in recent years. Demographic correlation analyses revealed that only the proportion of persons engaged in the lumber industry was positively correlated with the male maxillary sinus cancer mortality rate. A matched-pair case-control study was performed in Hokkaido in 1982; we collected data by questionnaires mailed to 41 male patients with maxillary sinus cancer and their age-, sex-, and residence-matched community controls and 82 males with laryngeal cancer and their community controls. Family, educational, and past histories of chronic sinusitis were not correlated with either maxillary sinus or laryngeal cancer. A cluster of occupations comprised of workers exposed to some chemical substances, coal miners, and tailors showed a significant elevated risk for maxillary sinus cancer but not for laryngeal cancer.—Natl Cancer Inst Monogr 69: 169–173, 1985.

Cancers of the nose, middle ear, and maxillary sinuses (ICD 160; nasal sinus cancer, hereafter) are relatively uncommon. However, the data gathered by the International Agency for Research on Cancer (*1*) show several cancer registries, i.e., those of São Paulo, Shanghai, Hong Kong, Poona (India), Doubs (France), Miyagi and Osaka (Japan) for men, and Shangai, Hong Kong, Poona, Neuchâtel (Switzerland), and Osaka for women recorded relatively high incidence rates around 1975. Japan shows a characteristically high proportion of maxillary sinus cancer (ICD 160.2) compared with other nations (*2*). Many investigators suggested some occupational risks of nasal sinus cancer but few researched Japanese workers (*3–7*).

In the present study, we collected occupational statistics by prefecture and correlated them with the maxillary sinus cancer mortality rates by prefecture. We also performed a case–control study of maxillary sinus cancer in Hokkaido, which is located in the northern part of Japan.

MATERIALS AND METHODS

The age-standardized mortality rates by prefecture were obtained in a previous study (*2*); we calculated similar rates for 1970 by the same method. From the Japanese Industrial Statistics Section, Research and Statistics Division, Minister's Secretariat, Ministry of International Trade and Industry, we obtained statistics of the numbers of persons engaged in manufacturing by intermediate industry group. These data are not sex specific and are not available for all prefectures; we were able to use data for only 9 of 20 industry groups for the present demographic correlation analysis. We calculated the proportion of all male and female workers (combined) engaged in each industry. A natural logarithmical transformation of the proportion that was applied improved its kurtosis or skewness. Demographic correlation analyses included a simple correlation, a partial correlation, and a multiple regression analysis.

A matched-pair case–control study was performed in Hokkaido in 1982. We mailed questionnaires to the subjects and requested information regarding their families, education, residences, occupation, histories of otorhinolaryngologic disease, and smoking habits. If necessary, telephone calls were made for additional information. We grouped the occupations as follows:

Dealers in asphalt, oil, wax, or other petroleum substances
Auto repair mechanics
Dealers in dye and chemical substances for industrial use
Miners of asbestos, coal, or other ores
Gilding, welding, or iron and steel workers
Plasterers or construction workers
Carpenters, joiners, and other woodworkers (e.g., furniture)
Workers in the boot and shoe industry, textile industry, and tailors

We selected 41 males with squamous cell maxillary sinus cancer from the 45 males with maxillary sinus cancer who were diagnosed at the Department of Oto-rhino-laryngology, Hokkaido University School of Medicine, during 1977 through 1981. We selected 2 hospital controls and 1 community control for each patient by matching on age, sex, and residence. The hospital controls were patients with laryngeal cancer who visited the same clinic during the same period. One hundred eleven laryngeal cancers were identified, and 108 of them were histologically classified as squamous cell cancer. From these 108 patients with laryngeal cancer, we selected 2 as hospital

ABBREVIATION: ICD = International Classification of Diseases.

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controls for each patient with maxillary sinus cancer. In addition, we also selected 1 community control for each laryngeal cancer patient. We selected community controls at random, using the telephone directory. Although we call the laryngeal cancer patient the hospital control for the one with maxillary sinus cancer, the data on maxillary sinus cancer patients were not compared with data from hospital controls but were compared with data from community controls. On the other hand, the data from patients with laryngeal cancer were compared with those from their community controls. The comparison was mainly by a subsequent univariate approach with 2×2 tables, and McNemar's test was used for statistical evaluation. Different occupations were clustered into certain occupational groups by the cluster analysis method.

RESULTS

The mortality rates of cancers of the nose, middle ear, and maxillary sinuses in Japan have shown a downward trend in recent years (table 1). Because maxillary sinus cancer mortality rates by prefecture account for 67 to 100% of all nasal sinus cancer in Japan (*2*), we used them for the present demographic correlation analyses. Figure 1 shows the prefectural variation of male maxillary sinus cancer mortality rates in 1980. Northern and southern parts of Japan tend to have relatively high rates. Prefectural mortality rates show a positive association; the corre-

TABLE 1.—*Mortality rates of cancer of nose, middle ear, and maxillary sinuses in Japan by site, sex, and year*[a]

ICD No.	Site	Sex	Yr		
			1970	1975	1980
160	Nose, middle ear, and maxillary sinuses	Male	1.4	1.2	0.9
		Female	0.8	0.6	0.4
160.2	Maxillary sinuses	Male	1.3	1.1	0.8
		Female	0.8	0.6	0.4

[a] Rates are age standardized by the direct method/100,000; population of all Japan in 1970 is the standard population.

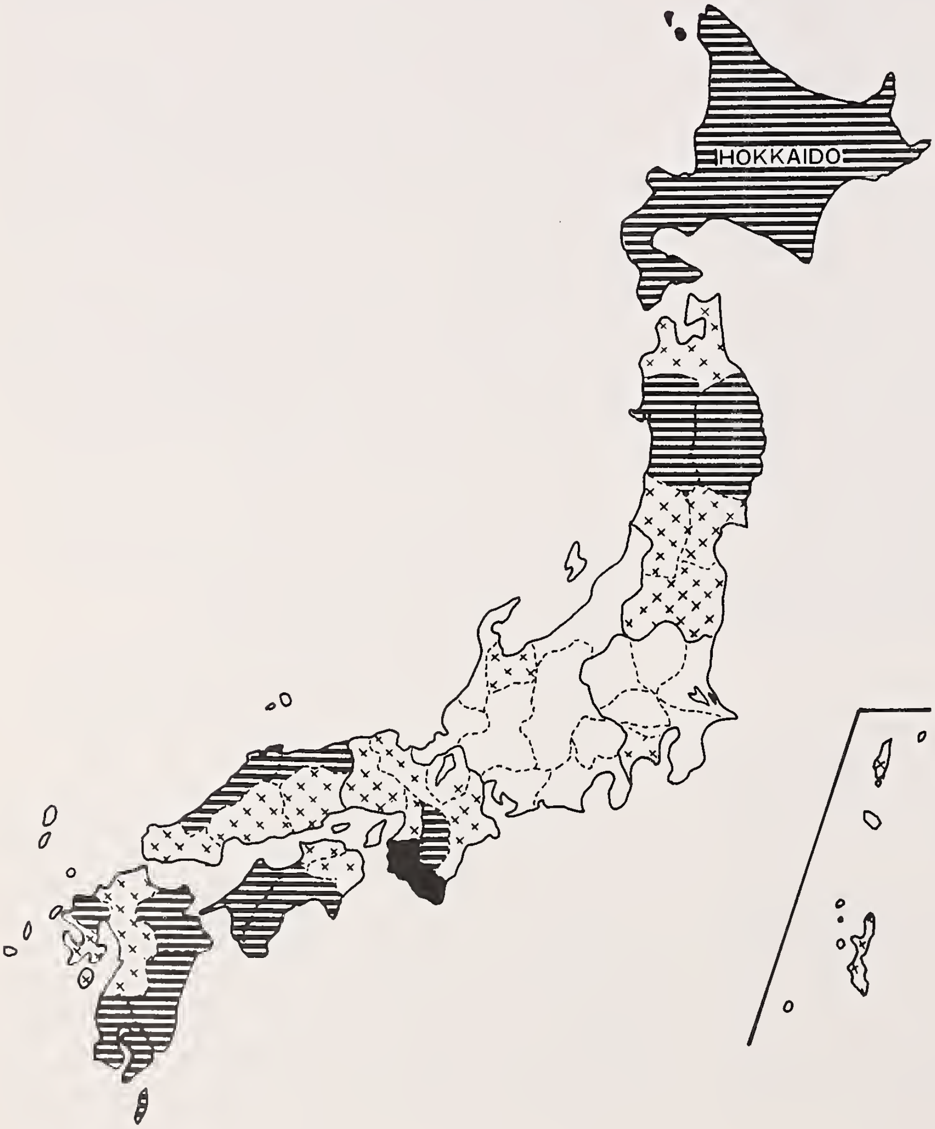

FIGURE 1.—Maxillary sinus cancer mortality rates of Japanese males by prefecture, 1980, age-standardized/100,000. *Open areas*= 0.4–0.6; *crosses in areas*=0.7–0.9; *lined areas*=1.0–1.2; and *solid areas*=1.3–1.6.

TABLE 2.—*No. of persons engaged in manufacturing by industry and year*

Population/workforce	Yr		
	1965	1970	1975
Population over age 15 (in millions)	72.9	78.9	84.5
Labor force (in millions)	47.9	51.5	53.2
Labor force participation rate, %	65.7	65.4	63.0
Persons engaged in manufacturing (millions)	9.9	11.7	11.3
Proportion of persons engaged in manufacturing (as percent of total labor force)	20.7	22.7	21.2
Persons engaged in manufacturing (in thousands)			
Food	1,099	1,140	1,172
Textile	1,327	1,264	996
Lumber	528	538	465
Furniture	250	304	315
Pulp	326	336	319
Publishing	411	468	494
Ceramic	499	572	557
Fabricated metal	653	844	855
Machinery	902	1,178	1,102

lation coefficient = 0.548 ($P<.05$) between rates for males for 1975 and those for 1980 but not for females for whom the correlation coefficient was 0.280 ($P>.05$). This association may indicate that prefectural mortality rates for maxillary sinus cancer among males show relatively stable secular changes compared with those for females during 1975 through 1980.

Table 2 shows the number of persons engaged in manufacturing in Japan by industry and year. During the last 10 years, the population over 15 years old increased from almost 73 to 85 million, and the number of persons engaged in manufacturing increased from 9.9 to 11.3 million. Workers in manufacturing comprise about 20% of the total labor force. Mean proportions of persons engaged in manufacturing are shown in table 3 with their kurtosis and skewness. These mean values of proportion do not sum to 100% because certain industry groups have been omitted. For a proportion to fit a normal distribution, its kurtosis should be close to 3 and its skewness close to 0. Most of the proportions did not fit a normal distribution in the original scale so we transformed them into a natural logarithmic scale. This transformation improved the skewness for most but not the kurtosis. We then proceeded to a demographic correlation analysis based on these transformed values.

The simple correlation coefficients between maxillary sinus cancer mortality rates among males in 1975 and 1980 and the transformed proportions of persons engaged in various industries are presented in table 4. The food industry shows statistically significant positive correlations with male maxillary sinus cancer mortality rates in cross-sectional and in time-lag correlations. Similar correlations can be seen for the lumber and publishing industries. The corresponding correlation coefficients with female rates are relatively smaller than those with male rates.

Although many industries show statistically significant correlations with mortality rates, partial correlation analyses revealed that only the proportions of persons engaged in the lumber industry (in its natural logarithmic scale) in 1970 and 1975 are significantly correlated with the male maxillary sinus cancer mortality rate in 1975 as shown in table 5. Multiple regression analyses also suggest the proportion of persons engaged in the lumber industry in 1970 and in 1975 to be the largest contributor to the variance of male maxillary sinus cancer mortality rates in 1975. The partial correlation coefficient between male mortality rate in 1975 and the proportion of workers in the lumber industry in 1965 is not statistically significant. However, a similar regression analysis of male mortality rates in 1975 on the proportions in 1965 also indicates that the proportion of workers in the lumber industry is the largest contributor to the male maxillary sinus cancer mortality rate in 1980. For female rates, we find no significant partial correlation with occupational proportions.

Twenty-one of 41 patients with maxillary sinus cancer and 20 of 82 with laryngeal cancer in the present case–control study were deceased as of September 1982. Rates of compliance, refusal, and no response to the request letter for the community controls were 41.3, 0.7, and 58.0%, respectively. Response rates for the maxillary sinus or laryngeal cancer patients were 100%. The mean ages for the maxillary sinus cancer patients, sinus cancer community controls, laryngeal cancer patients, and their

TABLE 3.—*Mean, kurtosis, and skewness of proportions of persons engaged in each manufacturing industry*[a]

Industry group	1965			1970			1975		
	Mean, %	Kurtosis	Skewness	Mean, %	Kurtosis	Skewness	Mean, %	Kurtosis	Skewness
Food	16.08	0.238	0.967	13.82	1.242	1.231	13.48	2.391	1.507
Textile	14.27	1.885	1.355	12.32	3.229	1.706	10.44	3.858	1.858
Lumber	8.85	5.230	1.931	7.48	5.198	1.912	6.22	3.765	1.597
Furniture	2.94	5.488	1.889	3.11	7.952	2.240	3.18	9.226	2.484
Pulp	3.52	5.778	2.247	3.11	5.909	2.301	2.93	3.804	1.874
Publishing	3.20	7.846	2.201	3.04	15.597	3.299	3.21	23.332	4.282
Ceramic	5.94	8.998	2.674	6.09	6.276	2.200	6.01	5.364	1.990
Fabricated metal	4.55	2.592	1.483	5.59	2.565	1.437	6.05	2.134	1.324
Machinery	7.26	−0.226	0.361	8.17	−0.527	0.176	8.00	−0.682	0.178

[a] Mean values do not total 100% because some industry groups have been omitted.

TABLE 4.—*Correlation between male maxillary sinus cancer mortality rates and natural logarithmically transformed proportions of persons engaged in industry*

Industry group	Maxillary sinus cancer mortality					
	1975			1980		
	1965	1970	1975	1965	1970	1975
Food	0.397[a]	0.481[a]	0.495[a]	0.403[a]	0.507[a]	0.484[a]
Textile	−0.446[a]	−0.271	−0.202	−0.281	−0.166	−0.087
Lumber	0.442[a]	0.502[a]	0.466[a]	0.365[a]	0.471[a]	0.454[a]
Furniture	0.013	0.052	−0.021	0.163	0.228	0.112
Pulp	0.072	0.171	0.154	0.173	0.276	0.206
Publishing	0.320[a]	0.346[a]	0.319[a]	0.325[a]	0.380[a]	0.299[a]
Ceramic	0.055	0.227	0.265	−0.172	0.021	0.076
Fabricated metal	−0.349[a]	−0.333[a]	−0.286	−0.305[a]	−0.360[a]	−0.352[a]
Machinery	−0.321[a]	−0.386[a]	−0.398[a]	−0.334[a]	−0.291[a]	−0.317[a]

[a] $P<.05$.

TABLE 5.—*Correlation between proportion of persons engaged in manufacturing lumber and wood products and maxillary sinus cancer mortality rates (age-standardized)*

Yr	Sex	Correlation analyses of proportion of persons engaged in manufacturing lumber and wood products during 3 periods					
		1965		1970		1975	
		Simple	Partial	Simple	Partial	Simple	Partial
1975	Male	0.442[a]	0.277	0.502[a]	0.362[a]	0.466[a]	0.328[a]
	Female	0.389[a]	0.116	0.341[a]	0.091	0.347[a]	0.138
1980	Male	0.365[a]	−0.028	0.471[a]	0.124	0.454[a]	0.184
	Female	0.136	0.149	0.113	0.185	0.136	0.149

[a] $P<.05$.

TABLE 6.—*Past history of chronic sinusitis in cancer cases and controls (matched analysis)*

Cancer site	Sinusitis history			Odds ratio	*P*
	Patients	Community control			
		Yes	No		
Laryngeal cancer					
Group 1	Yes	0	3	0.8	1.000
	No	4	34		
Group 2	Yes	2	3	0.6	.724
	No	5	31		
Maxillary sinus cancer	Yes	5	11	3.7	.061
	No	3	22		

TABLE 7.—*History of certain occupations (workers exposed to chemical substances, coal miners, and tailors) of cancer patients and controls*

Cancer site	Occupational exposure			Odds ratio	*P*
	Patients	Community control			
		Yes	No		
Laryngeal cancer					
Group 1	Yes	3	4	0.6	.546
	No	7	27		
Group 2	Yes	3	6	0.9	1.000
	No	7	25		
Maxillary sinus cancer	Yes	3	11	5.5	.027
	No	2	25		

TABLE 8.—*Current smoking status of cancer cases and controls*

Cancer site	Current smoker			Odds ratio	*P*
	Patients	Community control			
		Yes	No		
Laryngeal cancer					
Group 1	Yes	32	9	9/0	.002
	No	0	0		
Group 2	Yes	34	7	7/0	.008
		0	0		
Maxillary sinus cancer	Yes	35	2	0.5	.344
	No	4	2		

community controls were 59.2, 58.8, 61.7, and 61.1 years old, respectively.

The family, educational, and past histories of chronic sinusitis of these patients did not correlate significantly with either maxillary sinus or laryngeal cancer (table 6). A series of 2×2 tables failed to show any statistically significant association between each occupation and the cancers. Because a man may have several kinds of occupations during his lifetime, we applied a cluster analysis to the present data to assemble occupations into groups in which a man would be likely to be engaged during his life. Although it did not show a clear-cut clustering, these occupations could be grouped into a cluster of carpenters and plasterers; a cluster of dealers of petroleum substances, auto repair mechanics, and iron and steel workers; and a cluster of workers who were exposed to industrial chemicals and coal miners and tailors. This last cluster of occupations showed a significant association with maxillary sinus cancer but not with laryngeal cancer (table 7). Present smoking status was a significant risk factor for a person's developing laryngeal cancer but not for maxillary sinus cancer (table 8). Although there are some discrepancies in statistical significance between the two laryngeal cancer and community control comparisons, young age at start of smoking, long duration of smoking, and amount of daily smoking were associated with laryngeal cancer but not with maxillary sinus cancer.

DISCUSSION

In contrast to the mortality rates in 1975 of males with maxillary sinus cancer, those in 1980 did not associate with the natural logarithmically transformed proportions of persons engaged in manufacturing lumber and wood products in 1965, 1970, and 1975. The reason for this discrepancy is not clear. Similarly, it is not clear why the female mortality rates showed no association with the occupational indices. For a more productive demographic correlation analysis, we need more comprehensive data by prefecture than those we have at present.

Major industries in Hokkaido include agriculture, fishing, mining, and lumber. Hokkaido is a single prefectural region which, in 1980, had a population of 5.4 million. Medically, Hokkaido is a semi-closed or a self-contained area. Although no reliable statistics are available, it may be regarded that the Department of Oto-rhino-laryngology, School of Medicine, Hokkaido University takes care of more than one-half of the total number of patients with maxillary sinus cancer in Hokkaido.

Although chronic sinusitis has been suggested to be a risk factor for development of maxillary sinus cancer (*4, 7*), the present data are of borderline significance. The number of cases in the present case–control study was too small for us to examine associations between several potential risk factors by stratified analysis. Particularly, multiple occupational experiences of a single person could not be evaluated adequately. Therefore, although the present study suggests that a certain cluster of occupations may be related to maxillary sinus cancer, our results are only preliminary. Other findings of interest are the positive association between smoking and laryngeal cancer and the lack of association between smoking and maxillary sinus cancer.

A previous report (*5*) suggests that wood, bamboo, and grass and vine products workers are in occupations at high risk and that smoking; drinking of alcoholic beverages; and consumption of meat, green and yellow vegetables, or miso soup are related to the nasal sinus cancer risk (Hirayama T: Personal communication).

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Medical and Dental X rays as Risk Factors for Recently Diagnosed Tumors of the Head [1, 2]

Susan Preston-Martin, Brian E. Henderson, *and* Leslie Bernstein [3, 4]

ABSTRACT—We used epidemiologic data on 2 tumor sites, the intracranial meninges and the parotid gland, to evaluate the importance of medical and dental x rays as risk factors for radiogenic tumors of the head diagnosed among residents of Los Angeles County in recent years. Exposures to x-ray treatment to the head and to full-mouth dental x-ray series before 1960 appear to be risk factors for both meningiomas and parotid tumors. Evidence from both descriptive and analytic studies suggests that the female over male excess of meningiomas, which is greatest from ages 25 to 54 years, may be partially explained by the excess exposure of young women to dental x rays. Study participants' ability to recall diagnostic x rays accurately is also evaluated by our comparisons of interview data to those available from dental charts. Recall of these events appears to be unbiased and accurate enough to justify the use of interview data in investigations of these risk factors.—Natl Cancer Inst Monogr 69: 175–179, 1985.

From studies of exposed populations, we know that x rays and other forms of ionizing radiation can cause various tumors of the head and neck, and we know details of these associations. For example, cohorts of individuals, who as children received x-ray treatment for ringworm of the scalp, have developed excess benign and malignant intracranial tumors (*1*). Atomic bomb survivors show an excess of various head and neck tumors, including benign and malignant tumors of the salivary glands (*2*). Having approached this association from a different perspective, we will try to evaluate the importance of medical and dental x rays to the etiology of recently diagnosed tumors of the head in our geographically defined population in Los Angeles County.

We present epidemiologic data on 2 tumor sites, the intracranial meninges and the parotid gland, and also present findings from a validation study which compares data from patient interviews and from dental charts. Most of our epidemiologic data are gathered during interviews with patients and controls, and with this validation study, we evaluated whether these interview data can be used as the basis for comparison in a study of medical and dental x rays.

INTRACRANIAL MENINGIOMAS

Intracranial meningiomas are histologically benign neoplasms which account for 30% of all primary intracranial tumors (*3*). Our data on the epidemiology of intracranial meningiomas in Los Angeles came from 2 case–control studies, 1 in women (*4*) and 1 in men (*5*), and from incidence data for Los Angeles County from 1972 to 1981 (*6*). Methodologic details of these 3 studies are included in the papers referenced. Table 1 shows OR that relate meningiomas in women to exposure to full-mouth dental x-ray series. Information on whether the subject ever had a full-mouth series does not discriminate well between patients and controls because such a high proportion of all our subjects had this exposure. "All types of dental x-ray visits" was an even poorer discriminator because over 95% of the subjects had had their teeth x rayed. We do find an association between meningiomas in women and early exposure to full-mouth series, i.e., both when we define "early" as before age 20 (OR = 4.0) or as before 1945 (OR = 2.1). Because we only asked patients what age range they were in when they had their first full-mouth series we cannot tell more precisely whether the effect relates to exposure at an early age or during early calendar years when exposure dose was high (*7*).

The OR relating meningiomas in men to x-ray exposure variables are given in table 2. The strongest association was with x-ray treatment to the head before age 20 (OR = 7.0) for conditions such as acne and tinea capitis. (Unfortunately, the way we had asked the question about radiation treatment in the earlier study in women did not allow us to evaluate this variable.) We also found an association in the men with exposure to 5 or more full-mouth series before 1945 (OR = 2.7), although this was not statistically significant.

Because only those areas of the meninges at or below the tentorium are likely to be directly exposed during a full-mouth series, we also analyzed data from both studies by tumor location. Table 3 gives the cumulative exposure to full mouth dental x rays of patients with tentorial or subtentorial tumors compared with patients with supratentorial tumors. In both studies, a higher proportion of patients with meningiomas at or below the tentorium had exposure to more than 10 full-mouth series than did patients with tumors above the tentorium.

Figure 1 shows average annual age-specific incidence curves for intracranial meningiomas for Los Angeles

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ABBREVIATION: OR=odds ratio(s).

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TABLE 1.—*Meningiomas in women: OR for exposure to full-mouth dental x rays*[a]

Factor	Frequency in controls, %	OR	*P*
Ever had a full-mouth dental x-ray series	81	1.2	.71
Had more than 5 full-mouth x-ray series	27	1.6	.14
First full-mouth dental x-ray series before age 20	19	4.0	<.01
First full-mouth dental x-ray series before 1945	40	2.1	.03

[a] Data from supplementary sheet were received from both members of 101 patient neighbor pairs.

County for the 10 years from 1972 to 1981. Overall, women have higher rates than men, but this difference is not apparent until after they are 25 and declines after age 55 to the point at which rates for men and women 75 and older are similar. The number and percent of incident meningiomas diagnosed before death by age at diagnosis, sex, and tumor location are presented in table 4. For patients over age 55, the distribution by tumor location is the same for males and females; for those diagnosed under age 55, however, the proportion of tumors which arise at or below the tentorium is one-third higher in women compared with men. This observation fits well with the evidence that women, particularly those in the 15- to 29-year-old group, have their teeth x rayed more frequently than do men (*8*).

DENTAL X-RAY VALIDATION STUDY

We collected information from dentists for a subset of participants in a case–control study conducted to evaluate the relationship of dental x rays to tumors of the parotid gland (*9*). This validation study sought answers to 2 questions. 1) Is recall unbiased? That is, did these participants recall dental x rays equally well? 2) Are interview data accurate enough to be used as the basis for case–control comparison? We would expect recall of dental x rays to be even poorer than recall of medical x rays because dental x rays are more often routine than are the medical x rays, which are usually performed for diagnostic purposes of a specific clinical problem. Recall of low impact events such as painless routine procedures (e.g., most dental x rays) is known to be poorer than recall of health disorders (*10*). A similar validation study reported poor recall of prior diagnostic x rays (*11*). Subjects in this study failed to report 80% of the diagnostic x rays they had as outpatients during the previous 10 years, and the investigators concluded that "reliance on interview data alone could be completely invalid" (*11*). Nonetheless, we had hoped that through the

TABLE 2.—*Meningiomas in men: OR for x-ray variables*

Factor	Frequency in controls, %	Discordant pairs, case–control		OR	One-sided *P*
		+−[a]	−+[b]		
Had x-ray treatment to the head before age 20	1	7	1	7.0	.04
Had 5 or more full-mouth dental x-ray series before 1945	3	8	3	2.7	.11

[a] Values are No. of pairs in which the patient was exposed to the factor and the control was not.

[b] Values are No. of pairs in which the control was exposed to the factor and the patient was not.

TABLE 3.—*Cumulative exposure to full-mouth dental x rays of patients with tentorial or subtentorial tumors compared with patients with tumors at other intracranial sites*

Sex	Frequency of full-mouth dental x-ray series	No. of patients with meningiomas at:		OR
		Tentorial or subtentorial sites	Other sites	
Women				
	None	7	16	1.0[a]
	1–10	33	42	1.8
	>10	15	7	4.9
	Total	55	65	
Men				
	None	4	33	1.0[b]
	1–10	15	36	3.4
	>10	4	12	2.8
	Total	23	81	

[a] $P < .01$ in test for trend.

[b] OR (none vs. any) = 3.3; $P = .03$.

TABLE 4.—*Number and percent of incident cases of intracranial meningiomas diagnosed before death of Los Angeles County whites, 1972–81*

Age at diagnosis, yr	Meningioma location				Unknown		Total
	Tentorial or subtentorial		Other				
	No.	Percent	No.	Percent	No.	Percent	No.
<55							
Males	42	30	81	58	16	12	139
Females	104	40	132	50	26	10	262
>55							
Males	58	27	126	60	27	13	211
Females	123	27	275	60	57	13	455

rigorous use of highly specific questions and carefully devised probes, subjects would be able to recall providers of dental care and patterns of dental x-ray visits for different periods of their lives from childhood to the present.

We included 102 patients with parotid tumors and their 102 individually matched neighbor controls in the validation study [details of study methods and materials are described in the paper reporting findings (*9*)]. Both groups were similar in the number of dentists identified (434, 457, respectively) and in the number of interview and chart comparisons performed (142, 130, respectively). Complete dental charts from before the reference year (year of diagnosis of case minus 2) were available for 84 patients and 79 controls. Availability of complete dental charts decreased as the period of care became farther removed from the reference year. For dentists visited more than 20 years before the reference year (45.5% of all dentists) few complete charts were available (23 of 194 or 12%) from patients' dentists; 20 of 211 (9%) from those caring for controls.

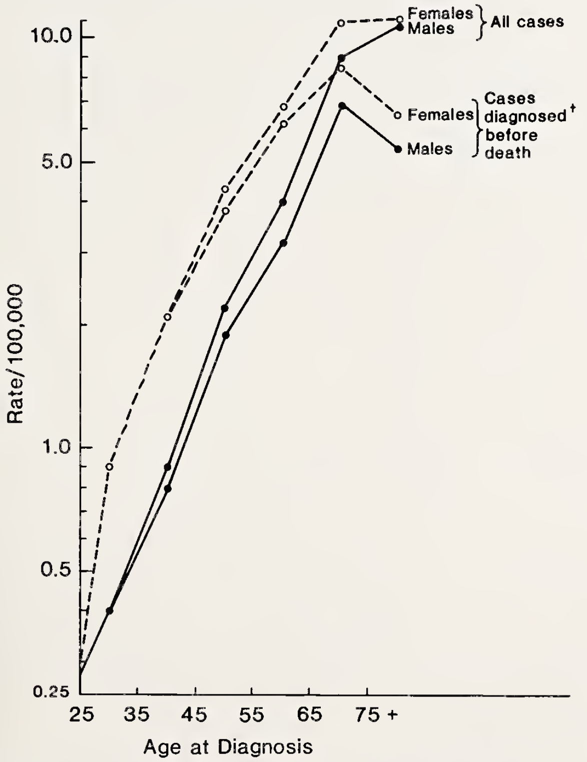

FIGURE 1.—Annual incidence of intracranial meningiomas in whites, Los Angeles County, 1972–81.

Table 5 shows similar patterns of agreement between interview and chart information on total number of x-ray visits and visits with full-mouth series during 2 periods for patients and controls. We compared case agreement with chart information with that of controls to determine if 1 group tended to overestimate or underestimate the number of x-ray and full-mouth visits more than the other group. The *P*-values for the general chi-square tests comparing the distributions (table 5) show that in each of the comparisons the distribution of agreement of case interview data with dental chart information is not significantly different from the distribution of agreement of control interview data with dental chart information. The mean difference between interview and chart estimates of numbers of x-ray visits in each of the 4 categories are all positive and are of similar magnitude for both groups of participants. Thus from our interview data, we see a consistent tendency for participants to overestimate their average number of x-ray visits [although we have a number of indications that the charts may represent underreporting of x rays (*9*)], but no indication that patients overestimate more than controls.

The most encouraging finding from our validation study is that overall recall appears to be unbiased because the measures of agreement between interview and dental chart data are similar for cases and controls. Recall accuracy, including completeness of recall, is far better than the 20% recall reported previously (*11*). Admittedly, however, if we used the precise number of various types of dental radiographic examinations, interview information would misclassify a high proportion of cases and controls. However, if we used interview information in our analyses with comparisons of extreme exposure categories or comparisons of fewer, wider exposure categories, then less misclassification would occur. We conclude that interview data may be used for case–control comparisons of dental x-ray exposure and that we would, because of unbiased misclassification, tend to underestimate the relative risks (*12, 13*).

TABLE 5.—*Dental x-ray validation study: Agreement between patient interview and dental chart on No. of x-ray visits*

Dentists first visited:	Reference year[a, b]							Mean difference	Chi-square comparison of distribution[c]
Within 20 yr of reference yr	≤−5	−4 to −2	−1	0	1	2–4	≥−5		
All x-ray visits									
Subject	5	16	23	25	17	19	8	+0.6	0.70
Control	3	17	12	25	14	20	10	+0.7	
Full-mouth visits	≤−3	−2	−1	0	1	2	≥3		
Subject	4	6	16	52	16	9	8	+0.4	0.37
Control	1	6	14	41	23	3	8	+0.5	
At least 20 yr before reference year	≤−5	−2 to −4	−1	0	1	2–4	≥5		
All x-ray visits									
Subject	0	1	1	5	3	2	5	+3.7	0.68
Control	0	0	3	8	2	1	5	+3.7	
Full-mouth visits		≤−2	−1	0	1	≥2			
Subject		1	2	5	3	5		+1.2	0.51
Control		1	1	10	4	2		+1.2	

[a] Reference year = year of diagnosis of case minus 2 yr.

[b] 0 indicates perfect agreement between patient and dental chart; −1 indicates underestimation by the patient by 1 x-ray visit; 1 indicates overestimation by the patient by 1 x-ray visit, if one assumes the chart is correct.

[c] Comparison of case and control distribution of agreement: Chi-square test: 2-sided *P*-value.

TUMORS OF THE PAROTID GLAND

Table 6 presents findings from our preliminary analysis of 304 case–control pairs from our epidemiologic study of tumors of the parotid gland which is currently in progress. Of the 304 patients included in this analysis, 78 had malignant and 226 had benign disease. We see a strong association with radiation exposure variables for malignant but not for benign parotid tumors. Risk of malignant disease is associated with prior radiation treatment to the head (OR = 3.0) and with exposure to 5 or more full-mouth series before 1960 (OR = 4.3).

The stronger association for malignant tumors is consistent with findings among atomic bomb survivors for whom relative risk estimates among the exposed were 9.8 for malignant parotid tumors and 2.0 for mixed tumors of the salivary gland (*2*). Radiation treatment has also been related to salivary gland tumors by case reports (*14*), clinical series (*15*), and cohort studies of individuals who received head and neck irradiation as treatment for benign childhood conditions (*16*).

TABLE 6.—*A case-control study of tumors of the parotid gland: Preliminary analysis of 304 pairs*

Type of radiation	Tumor type			
	Malignant		Benign	
	OR	*P*	OR	*P*
Treatment to the head	3.0	.03	1.5	.23
≥5 full-mouth x-ray series before 1960	4.3	.03	1.0	.49

These preliminary data are the first to implicate dental x rays in the etiology of this disease. In the U.S., the most commonly irradiated body site is the teeth (*8*). During 1970, 50% of the people living in the Western United States had their teeth radiographed (*8*). Most dental x-ray examinations involve direct exposure to the parotid gland. Average per film exposure in 1970 from intraoral examinations was 1,150 milliroentgens compared with 36 milliroentgens for chest films (*17*). Although few dosimetry data are available for x rays before 1960, 1 survey (done in Berkeley, California, in the 1950s) of dental x-ray machines in use at the time indicates that total skin exposure dose from a full-mouth series (113–315 rad) was in the range of what is regarded as a therapeutic dose for treatment of benign conditions (*7*). If we assume that the parotid dose was 10% of the total entrance dose (*18*), then in a single full-mouth examination, each parotid gland was exposed to 11 to 32 rad. If parotid tumors are related to dental x rays, we would expect those diagnosed in 1980 to be related to dental x rays which were taken before 1960, not only because these early x rays involved high exposure doses but also because the average latent period for parotid tumors is more than 20 years (*2*).

CONCLUSIONS

We found that patient recall of medical and dental x rays, especially of those performed decades ago for diagnostic purposes, is difficult to verify. Our investigation of diagnostic x rays in several case-control interview studies and our evaluation of the accuracy of such data in the dental x-ray validation study have led us, however, to further important conclusions about these difficult study variables. Interview information can be used in the study of x-ray exposure, but the way in which questions are asked is of critical importance. Also, early x-ray exposures appear to be important risk factors for tumors of the meninges and salivary glands diagnosed in recent years among the population of Los Angeles County.

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Occurrence of Second Primary Cancers Among Patients With Cervical Cancer in Osaka, Japan [1, 2]

Tomohiko Hiyama, Isaburo Fujimoto, Aya Hanai, *and* Akira Oshima [3]

ABSTRACT—Using the data accumulated in the Osaka Cancer Registry, we conducted a study on the effect of radiotherapy for cervical cancer in causing second primary cancers. Two groups of patients with cervical cancer, 1,767 who were given radiotherapy and 1,377 who were not, were followed for 7–9 years on average. In the radiotherapy group, 79 women had second primaries, and in the nonradiotherapy group, 23 did. These figures were compared with the expected cancer incidence for all sites. In the radiotherapy group, a significantly high observed-to-expected ratio was noted in cancers of the rectum, lung, and bladder. The nonradiotherapy group showed no site with a significantly high observed-to-expected ratio. Factors causing the increased level of lung cancer were studied. Some evidence indicated the excess was probably not related to smoking but to radiation, although the mechanism is unknown.—Natl Cancer Inst Monogr 69: 181–184, 1985.

Radiation therapy has been used widely for cervical cancer, especially for invasive cases, with a high cure rate. Thus it becomes necessary that the risks for second primary cancers among these survivors be estimated.

Boice et al. (*1*) and Smith (*2*) showed that radiation therapy for cervical cancer did not increase the risk of leukemia. Day (*3*) and Zippin and co-workers (*4*) observed second primary cancers at all sites among radiation-treated patients with cervical cancer and found significantly high risks demonstrated for several organs. These studies were conducted in the U.S., Canada, and in European countries. Our report deals with the incidence of second primary cancers arising in cervical cancer patients treated with or without radiation in Osaka, Japan, and a comparison with the results in Western countries.

MATERIALS AND METHODS

In Osaka, a population-based cancer registry has been operating since 1963 with the cooperation of the Osaka Medical Association, the Osaka Prefectural Health Department, and the Center for Adult Diseases. It serves all of Osaka, which had a population of 8.5 million in 1980. The Central Registry is located in the Center for Adult Diseases and registers data on cancer cases received from reports from hospitals and clinics and from death certificates from the Health Centers. As of April 1983, the Registry had 220,000 cases on file (*5*).

The number of incident invasive cervical cancer cases (ICD 180) in Osaka during 1966–70 was 3,496 (*6*). Among these, 109 cases were excluded because they were registered by death certificate only. From the remaining 3,387 who had been registered by notification reports from physicians or hospitals, the following patients were excluded: 1) 115 who died within 3 months after diagnosis of cervical cancer, and 2) 128 for whom no information on medical treatment was available. The remaining 3,144 were divided into 2 groups: the 1,767 and 1,377 patients who were treated with and without radiation therapy, respectively.

All patients in these 2 groups were followed up by collation with all death certificates of Osaka residents until the end of 1979. In calculating person-years at risk, we assumed the patients for whom a death certificate was not found were alive.

To define the second primary cancer, we modified the criteria presented by the International Agency for Research on Cancer (*7*). Furthermore, the second primary cancers occurring within 3 months after the date of diagnosis of cervical cancer were excluded in this study.

RESULTS

Clinical Features of the Observed Patients

Observed patients were classified by the age at diagnosis and the method of treatment (table 1). The radiotherapy group included a higher percentage of older women. These women were also classified by their clinical stage, as shown in table 2; those with localized disease were the most prevalent. However, the stage of many was unknown. The percentage of patients receiving radiotherapy was 47.5% in the localized group. It was higher in the advanced groups and exceeded 70% in the groups with "regional lymph node metastasis" and with "direct extension to adjacent organs."

Five- and 10-year relative survival rates of the 2 groups are presented in table 3 according to their clinical stage. The rates were similar between the radiotherapy and nonradiotherapy groups within each clinical stage. However, in the localized stage, the survival rate was higher in the group that was not given radiotherapy.

Second Primary Cancers Observed

We followed these patients with cervical cancer (table 1) routinely until the end of 1979. Total person-years for

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ABBREVIATIONS: ICD = International Classification of Diseases; O:E = observed to expected [ratio(s)].

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TABLE 1.—*No. of observed cervical cancer cases by age at diagnosis and method of treatment, 1966–70*

Age, yr	Radiotherapy		Nonradiotherapy		Total	
	No.	Percent	No.	Percent	No.	Percent
20–29	25	1.4	24	1.7	49	1.6
30–39	232	13.1	289	21.0	521	16.7
40–49	457	25.9	466	33.8	923	29.4
50–59	542	30.7	350	25.4	892	28.4
60–69	398	22.5	178	12.9	576	18.3
70–79	104	5.9	66	4.8	170	5.4
≥80	9	0.5	4	0.3	13	0.4
Total	1,767	100.0	1,377	100.0	3,144	100.0

both groups were similar. However, the patients given radiotherapy had a greater proportion of person-years in the older age groups. The average follow-up period was 7.2 and 9.0 years for the women with and without radiotherapy, respectively. The maximum follow-up period was 14 years for both groups.

Using the cancer incidence data of Osaka, we calculated the expected numbers of incident cancers at various sites, i.e., the person-years in each age and calendar-year group were multiplied by the appropriate cancer incidence rate at various sites among the general population in Osaka and summed. Table 4 shows the number of observed and expected second primary cancers in these 2 groups. A significantly high O:E of 1.46 was recorded for the radio-

TABLE 2.—*No. of cervical cancer cases by extent of disease and method of treatment, 1966–70*

Extent of disease	Radiotherapy		Nonradiotherapy		Total	
	No.	Percent	No.	Percent	No.	Percent
Localized	558	47.5	617	52.5	1,175	100.0
Regional lymph node metastasis	321	72.5	122	27.5	443	100.0
Direct extension to adjacent organs	292	78.3	81	21.7	373	100.0
Remote metastasis	24	68.6	11	31.4	35	100.0
Unknown	572	51.2	546	48.8	1,118	100.0

TABLE 3.—*Relative survival rates for patients with cervical cancer diagnosed in 1966–70*

Extent of disease	Relative survival rates, %			
	5 yr		10 yr	
	Radiotherapy	None	Radiotherapy	None
Localized	87	91	86	91
Regional lymph node metastasis	62	59	59	58
Direct extension to adjacent organs	43	35	38	38
Remote metastasis	35	36	39	40
Total	66	74	64	74

TABLE 4.—*The O and E second primary cancers by method of treatment*

Second primary site/type	No. of primary cancers					
	Radiotherapy			Nonradiotherapy		
	O	E	O:E	O	E	O:E
All sites	79	54.16	1.46[a]	23	44.17	0.52[b]
Buccal cavity	1	0.56	1.78	1	0.45	2.21
Esophagus	0	1.01	0	0	0.73	0
Stomach	16	16.23	0.99	5	12.65	0.40[b]
Colon	4	2.44	1.64	3	1.89	1.59
Rectum	9	1.87	4.82[a]	2	1.48	1.35
Liver	7	2.84	2.46	3	2.13	1.41
Lung	16	3.53	4.53[a]	4	2.62	1.53
Bone	0	0.18	0	0	0.14	0
Breast	3	4.76	0.63	1	4.54	0.22
Bladder	7	0.71	9.90[a]	1	0.51	1.98
Lymphoma	1	0.42	2.36	0	0.35	0
Leukemia	0	0.61	0	0	0.55	0

[a] $P<.01$.

[b] $P<.05$.

therapy group, whereas it was significantly low (0.52) for the nonradiotherapy group. Significantly high O:E were also seen for cancers of the rectum, lung, and bladder in the radiotherapy group: 4.82, 4.53, and 9.90, respectively.

The nonradiotherapy group had high O:E at 6 sites; however, all were below 2.21 and none were statistically significant. The O:E was significantly low for stomach cancer. The O:E of malignant lymphoma in the radiotherapy group was high but not significant, because of the small number of observed cases. No leukemia was found in the radiotherapy group; we expected 0.61.

Analysis of Second Primary Cancers

As second primary cancers, cancers of the rectum, lung, and bladder occurred more frequently in the radiotherapy group. In table 5, the observation period is divided into 4 categories: within 1 year, 1–4 years, 5–9 years, and 10 years or over, after diagnosis. All 9 patients in the radiotherapy group who had cancer of the rectum were observed 1–4 years. Therefore, we think the higher O:E might be caused by the radiotherapy or direct extension of cervical cancer, or both.

For bladder cancer, the O:E was highest within 1 year in both groups. After that, higher O:E were observed only in the radiotherapy group. None of the nonirradiated women developed bladder cancer.

The O:E for lung cancer in the radiotherapy group was highest (7.27) in the 1- to 4-year follow-up. In the periods 5–9 years and 10 years or over, the O:E were 3.66 and 2.13, respectively. In the nonradiotherapy group, a high O:E was observed only in the first 4 years. Table 6 shows the clinical information on the 16 patients in the radiotherapy group and the 4 in the nonradiotherapy group who developed lung cancer secondarily. Only 3 in the former group have histologic findings for cervical and

TABLE 5.—*The O and E second primary cancers by the period in year after diagnosis of cervical cancer*

Site	Parameter	Radiotherapy, yr				Nonradiotherapy, yr			
		1	1–4	5–9	10	1	1–4	5–9	10
Rectum	O	0	9	0	0	0	1	1	0
	E	0.19	0.60	0.84	0.24	0.11	0.21	0.66	0.29
	O:E	0	15.0	0	0	0	4.76	1.52	0
Bladder	O	2	3	1	1	1	0	0	0
	E	0.07	0.22	0.32	0.09	0.04	0.13	0.22	0.11
	O:E	28.6	13.64	3.13	11.11	25.0	0	0	0
Lung	O	1	8	6	1	0	3	1	0
	E	0.31	1.10	1.64	0.47	0.17	0	1.19	0.57
	O:E	3.23	7.27	3.66	2.13	0	4.41	0.84	0

TABLE 6.—*Medical information on lung cancer cases defined as second primary cancer*

Cervical cancer				Lung cancer		
Age at diagnosis, yr	Histology	Radiotherapy	Clinical stage	Interval of diagnosis		Histology
				Yr	Mo	
54	Squamous cell carcinoma	+	Localized	0	9	Unknown
56	″ ″ ″	+	Unknown	1	2	″
48	″ ″ ″	+	Localized	2	4	″
52	″ ″ ″	+	Unknown	2	6	″
74	″ ″ ″	+	Direct extension	2	8	″
56	″ ″ ″	+	Unknown	3	2	″
60	Unknown	+	Localized	3	6	″
42	Squamous cell carcinoma	+	Regional lymph node metastasis	4	0	″
41	″ ″ ″	+	Localized	4	9	″
61	″ ″ ″	+	Regional lymph node metastasis	5	5	Adenocarcinoma
55	Unknown	+	″ ″ ″ ″	5	10	Unknown
58	Squamous cell carcinoma	+	Unknown	6	7	″
41	″ ″ ″	+	Localized	8	0	″
51	″ ″ ″	+	Unknown	8	1	Adenocarcinoma
65	″ ″ ″	+	″	9	1	″
44	Unknown	+	″	10	4	″
68	″	—	″	2	4	Unknown
48	Squamous cell carcinoma	—	Localized	2	10	″
42	″ ″ ″	—	Unknown	3	2	″
52	Unknown	—	Regional lymph node metastasis	8	4	Squamous cell carcinoma

lung cancers. All were diagnosed as adenocarcinoma of the lung in the 5- to 9-year follow-up period.

The clinical stages of their cervical cancer are also described in table 6. Included in the radiotherapy group were 5 with localized disease, 3 with regional lymph node metastasis, 1 direct extension, and 7 whose stage was unknown. In the group not given radiation treatment, 1 had localized cervical cancer, 1 had regional lymph node metastasis, and the stage of 2 was unknown. No remarkable difference in the distribution of clinical stages was observed between these 2 groups. The clinical stages of the 3 patients with different histologic types in the radiotherapy group were as follows: 1 regional lymph node metastasis, and 2 stage unknown.

DISCUSSION

In our study, observed cervical cancer patients were followed by collation with all death certificates registered in the Osaka Prefecture. In some instances, the patients may have moved outside the Osaka Prefecture and died. However, all were assumed to be alive up to the end of the study period (1979). Therefore, this method tends to increase the person-years and the expected number of second primary cancers and to lower the O:E in table 4 below the actual figures to some extent. The O:E in table 4 should be assumed to be the smallest possible figure. However, the bias of such ratios is small, if one judges from the following observations.

In 1983–84, the Osaka Cancer Registry conducted an active follow-up on 10,746 registered patients diagnosed in 1975–76. Consequently we discovered 147 (1.4%) moved out of Osaka Prefecture.

These O:E (table 7) were compared with those in the studies conducted by Day (*3*) and Zippin (*4*). In these 3 studies, O:E for cancers of all sites, rectum, bladder, and lung were all significantly high in the radiotherapy group, with the single exception of bladder cancer in Zippin's series (it is high but not significantly so). High O:E for cancers of the rectum and bladder might be related to radiation, as Day and Zippin have already indicated.

Day and Zippin explained that the high O:E of lung cancer might be related to cigarette smoking or metastasis.

TABLE 7.—*Comparison of O:E for cancers of the selected sites in 3 surveys*

Radiotherapy	All sites	Rectum	Bladder	Lung	Investigator
Yes	1.7^a	4.1^a	2.4	3.2^b	Zippin (*4*)
Yes	1.1^a	1.7^a	3.4^a	2.4^a	Day (*3*)
No	1.0	1.4	1.2	2.2^a	"
Yes	1.5^a	4.8^a	9.9^a	4.5^a	Hiyama
No	0.5^b	1.4	2.0	1.5	"

[a] $P<.01$.
[b] $P<.05$.

However, in our study, a high O:E was observed only in the radiotherapy group. Furthermore, the histologic type of lung cancer in the 3 patients whose cervical cancer was histologically confirmed was adenocarcinoma, with different histologies from cervical cancer. These 3 lung cancers were diagnosed 5 years after the diagnosis of cervical cancer was made. These results suggest an association of a high incidence of lung cancer with radiation, although the mechanism is unknown.

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SESSION V

Cross-cultural Comparisons

Occurrence of Breast Cancer in Relation to Diet and Reproductive History: A Case–Control Study in Fukuoka, Japan [1, 2]

Tomio Hirohata,[3] Takao Shigematsu,[4] Abraham M. Y. Nomura,[5] Yasuo Nomura,[6] Akio Horie,[7] *and* Itsuyo Hirohata[3, 8]

ABSTRACT—An epidemiologic study on breast cancer in relation to diet and reproductive history was conducted with 3 populations at different levels of risk for the disease: Japanese in Fukuoka, Japan (low risk), Japanese in Hawaii (intermediate risk), and Caucasians in Hawaii (high risk). This report describes the Fukuoka portion of the study. We interviewed 212 patients with histologically confirmed breast cancer and an equal number each of hospital and neighborhood controls to determine risk factors for the disease. The results indicated that "overnutrition" (a high-fat and high-animal protein diet) was not statistically associated with the disease. As noted in previous studies, age at the first birth was positively related to the disease; those women who gave birth to their first child when they were 35 or more years of age showed a relative risk of 5.0 compared with those giving birth at less than 20 years of age. A past history of both natural abortion and of benign breast disease were significantly associated with the disease. On the whole, the results obtained from this Fukuoka portion of study were in good agreement with those from the Hawaii study during which Japanese and Caucasians in Hawaii were investigated.—Natl Cancer Inst Monogr 69: 187–190, 1985.

We initiated a cooperative epidemiologic study on breast cancer in Hawaii and Japan to investigate the etiologic role of possible risk factors in the causation of the disease. The risk factors studied were "overnutrition" (a high-fat and high-animal protein diet), exogenous estrogen intake, and other factors relating mainly to reproductive life of women. Three populations at different levels of risk for the disease were selected: Japanese in Fukuoka, Japan (low risk), Japanese in Hawaii (intermediate risk), and Caucasians in Hawaii (high risk). This report describes the study conducted in Fukuoka, Japan.

Some investigators suspected overnutrition to have an etiologic role in the causation of breast cancer on the basis of geographic correlation studies showing a high correlation between breast cancer mortality and per capita animal protein and fat consumption (*1, 2*). Animal experiments also suggested that high fat diets promote occurrence of breast tumor after carcinogens or initiating agents were administered (*3*). Thus we conducted the present cooperative case–control study to confirm whether overnutrition plays any role in the causation of breast cancer in humans. Furthermore, several additional risk factors (mainly relating to reproductive life) were examined.

MATERIALS AND METHODS

We identified 212 female breast cancer patients in 5 major hospitals in Fukuoka area: National Kyushu Cancer Center Hospital, Kyushu University Hospital, Fukuoka University Hospital, Kurume University Hospital, and the National Fukuoka Central Hospital. For each patient, 2 sex- and age-matched (within 5 yr) controls were selected. One was a hospital control who had no cancer and no benign breast disease. The other was a neighborhood control who was randomly chosen from electoral listings. The patients and controls were interviewed at their homes regarding their dietary histories before onset of the disease, their reproductive histories, etc. Thus 212 triplets were interviewed. The response rate was 98.6% for patients, 96.5% for hospital controls, and 86.6% for neighborhood controls. In addition, we reinterviewed about 11% or 69 women who were selected at random to examine reproducibility of their dietary histories.

RESULTS AND DISCUSSION

Table 1 shows the animal protein intake from various food sources of patients and hospital or neighborhood controls; their average animal protein intake per week was similar. Further breakdown of animal protein intake according to various food sources showed similar results. No significant differences were observed either between patients and hospital controls or between patients and neighborhood controls, with the exception that patients consumed more animal protein from shellfish than did hospital controls ($P<.05$).

The same analysis was done for fat intake, and the results are presented in table 2. Average intake of total fat per week was nearly identical for all: 358, 361, and 362 g

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ABBREVIATION: RR = relative risk(s).

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TABLE 1.—*Average animal protein intake from various food sources*

Protein source	Mean intake, g/wk		
	Patients	Hospital controls	Neighborhood controls
Total animal protein	278	272	264
Eggs	29	29	27
Milk and milk products	25	29	21
Fish and marine products	122	114	123
Fresh fish	45	44	46
Shellfish	21[a]	17	20
Processed	56	52	57
Meat, poultry, and products	88	88	85
Fresh	80	80	77
Processed	8	8	8
Food eaten outside the home	14	12	8

[a] $P < .05$, patients vs. hospital controls.

TABLE 2.—*Average fat intake from various food sources*

Fat source[a]	Mean intake, g/wk		
	Patients	Hospital controls	Neighborhood controls
Total fat	358	361	362
Animal fat	164	168	163
Vegetable fat	177	180	190
Eggs	26	26	24
Milk and milk products	28	32	24
Fish and marine products	22	21	22
Meat, poultry, and products	73	74	76
Fresh	64	65	67
Fats and oils	167	174	181
Animal origin	15	16	17
Vegetable origin	151	158	164
Soybean products	26	22	26
Food eaten outside the home	17	13	9

[a] Fat eaten outside the home was not separated into animal or vegetable origin.

for patients, hospital controls, and neighborhood controls, respectively. Total fat was subdivided into animal and vegetable fat. Again, no essential differences were noted between patients and controls. Fat intake was subsequently subdivided according to various food sources, and none of these comparisons showed any significant differences.

Besides the analysis of average amount of nutrient intake, we examined distribution of nutrient intakes. All women were subdivided into 4 quartiles, and RR of the patients for the second, third, and fourth quartiles compared with the first quartile were computed by multiple logistic regression analysis (*4*). The RR with 95% confidence intervals were presented for all women in table 3 and for postmenopausal women in table 4. For this analysis, hospital and neighborhood controls were combined into 1 control group because differences between them were small.

As seen in table 3, RR were close to unity and none of them exceeded 2.0. No dose-response relationship was observed. However, 9 of the 12 RR in the table were more than unity, and 2 of them (the third quartiles of both animal protein and fat intakes) were significantly so. Thus we see no clear evidence that higher intake of both animal protein and fat are associated with breast cancer.

It has been hypothesized that overnutrition might be associated particularly with postmenopausal breast cancer patients (*5*). The findings given in table 4 of postmenopausal women were essentially the same as those in table 3. The RR computed were close to unity, and again we see no clear evidence that higher intake of animal protein and animal fat are associated with postmenopausal breast cancer.

Assessment of dietary intake is much more difficult than that of smoking or drinking habits. Therefore, we selected a sample of approximately 11% or 23 triplets (69 women) and reinterviewed them to assess reproducibility of dietary intake. For the group, the reproducibility was high. The average intake of nutrients estimated based on the second interview were within 5% of the estimates obtained from the original interview. Thus we believe that our method for taking the dietary histories was acceptable for our study.

Besides dietary intake, possible risk factors relating to reproductive life, etc., were examined. Table 5 shows the distribution of patients, hospital controls, and neighborhood controls by number of live births. Hospital and neighborhood controls showed similar distributions, but far more patients were nulliparous and far fewer had 4 or more children. The fact that breast cancer patients tended to have fewer children has been reported by numerous

TABLE 3.—*The RR and 95% confidence intervals for all participants*[a]

Quartile	Animal protein		Total fat		Animal fat		Vegetable fat	
	RR	Confidence interval	RR	Confidence interval	RR	Confidence interval	RR	Confidence interval
Second	.99	0.60–1.64	1.33	0.81–2.19	1.53	0.93–2.50	1.01	0.62–1.65
Third	1.68	1.03–2.76	1.08	0.65–1.79	1.88	1.13–3.13	.82	0.50–1.34
Fourth	1.12	0.65–1.93	1.01	0.60–1.71	1.28	0.75–2.18	.75	0.45–1.24

[a] Risks were computed relative to the first quartile and adjusted for age, weight, menopause, and parity by multiple logistic regression analysis. Hospital and neighborhood controls were combined.

TABLE 4.—*The RR and 95% confidence intervals for postmenopausal women*[a]

Quartile	Animal protein		Total fat		Animal fat		Vegetable fat	
	RR	Confidence interval	RR	Confidence interval	RR	Confidence interval	RR	Confidence interval
Second	1.36	0.72–2.56	1.64	0.89–3.04	1.51	0.84–2.71	.90	0.50–1.62
Third	1.46	0.81–2.65	1.02	0.56–1.86	1.76	0.96–3.24	1.03	0.58–1.85
Fourth	.95	0.49–1.86	1.04	0.55–1.97	1.17	0.62–2.19	.61	0.33–1.12

[a] Risks were computed relative to the first quartile and adjusted for age, weight, and parity by multiple logistic analysis. Hospital and neighborhood controls were combined.

TABLE 5.—*Distribution by number of live births*[a]

Participants	No. of live births					
	0	1	2	3	≥4	Total
Patients						
No.	49	23	59	42	39	212
Percent	23.1	10.8	27.8	19.8	18.4	100
Hospital controls						
No.	24	31	43	58	56	212
Percent	11.3	14.6	20.3	27.4	26.4	100
Neighborhood controls						
No.	26	28	55	34	69	212
Percent	12.3	13.2	25.9	16.0	32.5	100

[a] $\chi^2 = 31$; $P < .001$.

previous epidemiologic studies. Patients were significantly older at the birth of their first child (25.6 yr) than were hospital (24.6 yr; $P < .05$) or neighborhood controls (24.7 yr; $P < .05$) as MacMahon (*6*) reported.

Because these 2 variables, parity and age at first birth, were closely associated, we tried to separate the effect of 1 variable from the other. The RR of each variable adjusted for the other by the Mantel-Haenszel method (*7*) are presented in table 6. As shown, RR by age at first birth increased with increasing ages, and a dose–response relationship was clear. On the other hand, such a tendency was not observed for parity, and a dose–response relationship was unclear. Thus we see that age at first birth was a more consistent risk factor than was parity.

We further computed RR and 95% confidence intervals of selected other variables by multiple logistic regression analysis. Variables selected were smoking, family history of cancer, history of benign breast disease, hysterectomy, abnormal menses, induced or natural abortion, age at menarche, age at first birth, and exogenous estrogen use. Both unadjusted and adjusted RR are listed in table 7. When adjustment was done, all other selected factors were taken into account. Adjustment for other factors generally had little effect on the magnitude of the RR.

Factors found to have a significant association with breast cancer were: past history of benign breast disease, past history of natural abortion, and age at first birth. All other selected factors showed no significant association with the disease. However, age at menarche showed suggestive evidence that older ages at menarche were associated with decreasing risk for the disease. Past history of abnormal menses was associated with breast cancer before adjustment, but this became insignificant after adjustment for other factors. Although exogenous estrogen intake was not associated with the disease, few women in Fukuoka took estrogens after menopause, so that the present results

TABLE 6.—*The RR by age at first birth and parity*

Parity	Age at first birth, yr				
	20–24	25–29	30–34	35+	RR[a]
1	1.00	1.17	1.33	2.50	1.00
2	1.75	1.77	2.67	0.95	1.74
3+	1.15	1.91	1.00	—	1.26
RR[b]	1.0	1.44	1.25	2.91	

[a] The RR were adjusted for age at first birth by the Mantel-Haenszel method.

[b] The RR were adjusted for parity by the Mantel-Haenszel method.

TABLE 7.—*The RR and 95% confidence interval associated with selected variables*

Selected variable	Unadjusted		Adjusted[a]	
	RR	Confidence interval	RR	Confidence interval
Smoking	.86	0.50– 1.47	.80	0.50– 1.29
Family history of cancer	1.03	0.50– 2.12	.96	0.65– 1.42
Benign breast disease	2.72	1.29– 5.72	2.69	1.19– 6.08
Hysterectomy	1.45	0.90– 2.34	1.21	0.73– 1.99
Abnormal menses	2.58	1.17– 5.69	2.20	0.95– 5.10
Age at menarche, yr[b]				
14–15	.81	0.48– 1.35	.73	0.44– 1.21
16–17	.78	0.45– 1.36	.69	0.41– 1.17
18+	.54	0.24– 1.21	.50	0.23– 1.08
Induced abortion	1.19	0.75– 1.89	1.52	0.93– 2.48
Natural abortion	1.53	1.01– 2.30	1.91	1.20– 3.02
Estrogen intake	1.29	0.76– 2.19	.84	0.48– 1.45
Age at first birth, yr[c]				
20–24	1.59	0.41– 6.16	1.56	0.55– 4.39
25–29	2.20	0.68– 7.06	2.37	0.83– 6.77
30–34	2.04	0.49– 8.51	2.07	0.62– 6.89
35+	4.20	0.59–29.99	5.04	0.97–29.09
Nulliparous	4.11	1.38–12.24	5.55	1.82–16.88

[a] The RR were adjusted by the multiple logistic regression method.

[b] Ages ≤ 13 yr were taken as the standard.

[c] Ages ≤ 19 yr were taken as the standard.

did not exclude the possibility that estrogen intake for replacement after menopause might be associated with the disease.

Past history of benign breast disease was clearly a risk factor. History of natural abortion also seemed to be associated with the disease. The RR of age at first birth increased with increasing ages. Risks of those women who had their first child when they were more than 35 years of age reached an unadjusted risk of 4.20 and an adjusted one of 5.04, which were close to risks observed among nulliparous women.

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Breast Cancer in Caucasian and Japanese Women in Hawaii [1, 2]

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ABSTRACT—This case-control study included 183 Japanese and 161 Caucasian patients with breast cancer and equal numbers of matched hospital and neighborhood controls. The following factors were found to be associated with increased breast cancer risk in both groups of women: family history of breast cancer, history of benign breast disease, early age at menarche, late age at first childbirth, and late menopause. We noted a weak suggestion that the patients ate more saturated fats and oleic acid and took replacement estrogens for a longer period than did the neighborhood, but not hospital, controls. However, none of these differences was statistically significant. — Natl Cancer Inst Monogr 69: 191–196, 1985.

In Hawaii, Caucasian women have almost a twofold greater risk for breast cancer than do women of Japanese ancestry even though they live in the same environment (*1*). Because of this difference, we conducted the present study to identify risk factors related to breast cancer in these 2 distinct population groups

MATERIALS AND METHODS

The patients were women of Caucasian or Japanese ancestry, 45 to 74 years old, who were first diagnosed between 1975 and 1980 at any one of the 7 largest community hospitals on the Hawaiian island of Oahu. They were systematically identified by study staff members who monitored the pathology departments of each of the cooperating hospitals. In addition, an annual record linkage was done with the Statewide Hawaii Tumor Registry so that the chance of missing any newly diagnosed patients who qualified for the study was reduced. The diagnosis of breast cancer was confirmed by a review of each patient's histologic slides by a team of pathologists.

For each patient, 1 hospital and 1 neighborhood control neither of whom had ever had breast cancer were recruited. Both sets of controls were matched to the patients by sex, race, age within 5 years, and Oahu residency. Hospital controls were additionally matched by time of hospitalization and, in most instances, the admitting hospital. These controls were hospitalized for a variety of diseases:

Disease	Percent
Circulatory	18.6
Digestive	17.4
Genitourinary	9.7
Central nervous system	8.6
Musculoskeletal and connective tissue	8.3
Respiratory	5.7
All others	31.7

Potential hospital controls who were diagnosed with benign breast disease or with any cancer were excluded from the study. Neighborhood controls were identified by means of an algorithm based on the use of the cross-reference telephone directory which reaches approximately 90% of the households on Oahu. In most instances, the neighborhood controls lived in the same census tract as their matched patients.

Whenever a potential control was not interviewed, she was replaced by another woman chosen in the same manner. In this way, patients and controls were matched for their willingness to participate in the study. The reasons for nonparticipation are presented in table 1. Except for Caucasian hospital controls, the participation rates were fairly comparable between patients and their respective controls. The severity of a patient's illness was the most frequent reason for physician refusals.

Trained female interviewers conducted almost all interviews in the homes of the subjects. To minimize possible interviewer bias, 1 person interviewed each set of 1 patient and 2 matched controls. For the drug history portion of the interview, the interviewer asked each woman if she had ever taken replacement menopausal estrogens for a month or longer for any of a number of different conditions. If the response was affirmative, the interviewer showed the woman samples of over 30 estrogen preparations to assist her in her recall. The month and year of initial use and the duration of use of each preparation were then recorded. A signed consent was requested from the subject authorizing the study nurse to contact her physician to verify the medication history, which included information on the use of other drugs besides estrogens. With the additional

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TABLE 1.—*Interviews attempted and completed among Caucasian and Japanese subjects in Hawaii from 1975 to 1980*

Subjects	Interview status	Patients		Hospital controls		Neighborhood controls	
		No.	Percent	No.	Percent	No.	Percent
Caucasian	Total selected for interview	198	100.0	231	100.0	185	100.0
	Not interviewed due to:						
	Physician refusals	8	4.0	32	13.9	0	0
	Subject refusals	29	14.7	38	16.5	24	13.0
	Total interviewed	161	81.3	161	69.7	161	87.0
Japanese	Total selected for interview	218	100.0	227	100.0	211	100.0
	Not interviewed due to:						
	Physician refusals	8	3.7	10	4.4	0	0
	Subject refusals	27	12.4	34	15.0	28	13.3
	Total interviewed	183	83.9	183	80.6	183	86.7

information obtained from the physician or his/her office staff, a conference was then held with the interviewer, nurse, and study physician to review the level of agreement between the 2 sources of information. Sometimes the patient stated that she did not take the estrogens even though her physician prescribed them. On other occasions, the patient did not realize she was taking estrogens which, according to her physician's records, had been prescribed. At times, the subject or the personal physician had to be recontacted to clarify the information. The final decision on the accuracy of the information was made by the study physician who did not know at the time if the subject was a patient or a control.

The date of diagnosis of the case was the reference date for each case–control set. Thus for both patients and matched controls, information recorded on certain variables was limited to the period prior to the reference date. In addition to the use of replacement estrogens, these variables included past history of benign breast disease, family history of breast cancer, age, and menopausal status.

The interview also included a dietary history based on a selected list of 43 food items that represented the major sources of total and saturated fat, cholesterol, and animal protein in this population. Quantitative intakes were assessed with the aid of colored photographs showing prepared foods in 3 serving sizes. The structured interview consisted of an item-by-item recall so that we obtained the frequencies and amounts of foods consumed in a usual week. For patients, the period was a usual week before diagnosis, whereas, for controls, the period was a usual recent week. Mean nutrient intakes were computed from the reported amounts of foods consumed, with the use of standard food composition tables (*2–8*). A further description of this method and its reproducibility have been reported elsewhere (*9*).

The association of the dietary exposure variable with breast cancer risk was evaluated by comparisons of the mean values between patients and controls as well as by the risk ratios. The case–control comparison of the mean intake of each nutrient, statistically adjusted for selected potential confounding variables, was done by multiple covariance analysis (*10*). The risk ratio and its variance

TABLE 2.—*Single-factor age-matched risk ratio for selected characteristics related to breast cancer among Caucasian and Japanese subjects in Hawaii, 1975–80*[a]

Characteristics	Caucasian		Japanese	
	Risk ratio	95% Confidence limits	Risk ratio	95% Confidence limits
History of benign breast disease				
No	1.0		1.0	
Yes	1.9	1.2–3.0	2.3	1.4–3.7
History of breast cancer in mother and sisters				
No	1.0		1.0	
Yes	1.4	0.7–2.8	4.3	2.0–9.5
Menopausal status				
Natural	1.0		1.0	
Surgical	.9	0.6–1.4	0.8	0.5–1.3
Premenopausal	2.2	0.9–5.5	2.3	1.1–4.9
Age at menopause, yr				
<40	1.0		1.0	
40–45	1.2	0.6–2.1	1.5	0.7–3.2
≥46	1.5	0.8–2.5	1.6	0.8–3.2
Premenopausal	2.4	1.1–5.1	2.9	1.3–6.3
Age at first birth, yr				
<20	1.0		1.0	
20–24	1.5	0.7–3.0	2.0	0.9–4.5
25–29	1.6	0.8–3.4	2.0	0.9–4.4
≥30	2.9	1.3–6.5	2.5	1.1–6.0
Nulliparous	2.0	1.0–4.1	2.8	1.2–6.9
Age at menarche, yr				
≥15	1.0		1.0	
14	2.2	1.1–4.6	1.3	0.7–2.4
13	1.8	0.9–3.5	1.2	0.7–2.2
≤12	1.6	0.8–3.1	1.2	0.7–2.1

[a] Risk ratios were estimated by conditional logistic regression analysis for matched case-control data (*11*). The hospital and neighborhood controls were combined.

TABLE 3.—*Case-control comparisons of nutrient intakes by race with multiple covariance analysis*[a]

Subjects	Nutrient	Hospital			Neighborhood		
		Patients	Controls	*P*	Patients	Controls	*P*
Japanese	Calories, wk	5,524	5,409	.96	5,557	5,182	.32
	Total fat, g/wk	363	355	.97	365	338	.26
	Saturated	121	116	.75	121	112	.30
	Oleic acid	142	137	.80	143	130	.14
	Linoleic acid	67	69	.49	68	65	.62
	Total protein, g/wk	280	270	.57	280	260	.14
	Animal	255	246	.55	254	236	.12
	Vegetable	25	24	1.00	26	24	.94
	Cholesterol, mg/wk	1,755	1,760	.69	1,749	1,649	.29
Caucasian	Calories, wk	6,415	6,926	.26	6,478	6,297	.50
	Total fat, g/wk	430	442	.82	433	406	.19
	Saturated	150	157	.60	152	141	.15
	Oleic acid	159	165	.71	160	150	.19
	Linoleic acid	83	80	.46	84	80	.35
	Total protein, g/wk	332	333	.98	333	333	.99
	Animal	305	299	.67	305	304	.92
	Vegetable	27	34	.11	28	29	.77
	Cholesterol, mg/wk	1,982	2,038	.66	1,986	1,881	.37

[a] Adjustment was made simultaneously for age, age at first birth, age at menopause, history of benign breast disease, and family history of breast cancer.

were estimated by conditional logistic regression analysis for matched case-control data (*11*); the case-control status was taken as the response variable, and the primary exposure variable and potential confounding variables were entered as regressor variables.

RESULTS

The average ages of the 183 Japanese women with breast cancer, their matched hospital controls, and neighborhood controls were 56.8, 56.9, and 56.7 years, respectively. For the 3 corresponding groups of Caucasian subjects, the average ages were 60.3, 60.6, and 60.9 years, which indicates the success of the age-matching procedure.

The risk ratios for several important factors of breast cancer are presented in table 2. Because preliminary analysis showed that the findings for hospital and neighborhood controls were reasonably comparable for these variables, we combined the 2 sets of controls in this analysis. For Caucasian breast cancer patients, significant risk ratios were observed for past history of benign breast disease, premenopausal status, late age at first birth or nulliparity, and early age at menarche. For the Japanese, significant risk ratios were observed for past history of benign breast disease, positive family history of breast cancer, premenopausal status, and late age at first birth or nulliparity. Surgical menopause, relative to natural menopause, had a negative association, but it was not significant. The magnitudes of the risk ratios for the Caucasian and Japanese subjects were fairly similar, except for the family history of breast cancer and age at menarche.

The results of our comparing patients with each control group separately by their nutrient intakes are presented in table 3. Multiple covariance analysis was done with simultaneous adjustment for age, age at first birth, age at menopause, history of benign breast disease, and family history of breast cancer. The analysis suggested that Japanese and Caucasian patients ate more saturated fat and oleic acid than did their corresponding neighborhood controls (but the differences were not statistically significant)

TABLE 4.—*Breast cancer risk according to duration of menopausal estrogen use by race and source of controls*[a]

Source of controls	Duration of use, mo	Caucasian		Japanese	
		Risk ratio	95% Confidence limits	Risk ratio	95% Confidence limits
Neighborhood	1–12	0.9	0.4–2.0	2.4	1.3–4.7
	13–72	0.7	0.4–1.5	0.7	0.3–1.5
	≥73	1.3	0.7–2.6	1.9	0.8–4.4
Hospital	1–12	0.5	0.2–1.0	1.0	0.6–1.8
	13–72	1.4	0.6–2.9	0.6	0.3–1.2
	≥73	0.8	0.4–1.6	1.2	0.6–2.4

[a] Risk was calculated relative to nonusers of menopausal estrogens and statistically adjusted for history of benign breast disease, family history of breast cancer, age at first birth, and age at menopause by conditional logistic regression analysis (*11*).

and that Japanese patients ate more animal protein than did their corresponding neighborhood controls.

The association of replacement estrogens with breast cancer, based on duration of use, is shown in table 4. Simultaneous adjustment was done for the same variables as in table 3, except age, by conditional logistic regression analysis. Although no clear dose–response trends in the relative risk were seen for breast cancer in the 2 ethnic groups, there was a suggestion in the neighborhood control comparison that patients were more likely to have had a long duration of estrogen use (≥73 mo).

DISCUSSION

Studies of migrants have usually shown that the breast cancer rates of relocated women have shifted from the low rates prevailing in their country of origin toward the high rates prevailing in their host country (*12, 13*). This pattern is particularly evident in the women of Japanese ancestry living in the U.S. (*14, 15*) who have a different life-style than their counterparts living in Japan. Available data indicate that Japanese women in Hawaii have 2.5 times the risk for breast cancer than their peers in Japan (*1*). These observations indicate that environmental factors play a larger role than do genetic factors in determining breast cancer risk. In comparison to the Japanese, Caucasian women in Hawaii have a high incidence rate of breast cancer which is comparable with the rates among other U.S. white women (*1*). During the period 1973–77, Caucasian women in Hawaii had an average annual breast cancer incidence rate of 228/100,000 for ages 45 to 74. For Japanese women in Hawaii, the comparable rate was 118, or about one-half the rate in Caucasians (Hawaii Tumor Registry Staff: Personal communication).

Based on the findings in this study, Hawaii Caucasian women have the following risk factors for breast cancer: a past history of benign breast disease, late menopause, late age at first childbirth or nulliparity, and early age at menarche. These same factors have been repeatedly identified in other U.S. white women by other investigators (*16–21*). The Japanese women in Hawaii have similar risk factors for breast cancer as the Caucasian women but with some differences. In particular, a history of breast cancer in mother or sisters was a significant factor for the Japanese but not the Caucasians. Other researchers (*22, 23*) have usually observed that women with a family history of breast cancer were at increased risk for the disease. The fact that the association in Caucasian cases was in the expected direction, though not statistically significant, is in support of this observation. The age at menarche was a significant factor for only Caucasian women, but the trends for both ethnic groups were erratic. Numerous case–control studies have shown an increased breast cancer risk with early menarche (*21, 24–27*). However, the differences were small in some studies (*18, 28*) and 3 groups of workers (*29–31*) reported no association. Limitations among women in their accuracy of recalling the age at menarche (*32*) probably have contributed to the different findings in the past studies. However, the consistent direction of the association, when it is present, seems to indicate that the relationship does exist.

Experimental studies have shown that a high-fat diet can promote mammary tumor production (*33–35*), and human correlational studies have suggested an association between high fat intake and breast cancer risk (*36–38*). However, analytical studies in humans have produced equivocal findings. In Canada, Miller et al. (*39*) found that patients with breast cancer consumed more fat than did controls, but the relative risks were close to unity and none of them was statistically significant. Furthermore, no dose–response relationship was observed. Graham and associates (*40*) examined dietary records of a large number of breast cancer patients and controls in New York and found no significant differences in fat and animal fat consumption between the 2 groups. Lubin et al. (*41*) reported differences between patients with breast cancer and controls in their dietary intake, but the relative risks were only 1.5 for beef, 2.2 for pork, and 1.5 for sweet desserts. The intake of separate nutrients was not estimated.

In the present study, we found no substantial differences in the dietary intake of fat, proteins, or cholesterol between patients and controls. It could be argued that neighborhood controls may be a more suitable group than are hospital controls in this study because hospital controls have diseases that are related to dietary patterns. However, that the cases consumed more saturated fat and animal protein than even the neighborhood controls was only weakly suggested. Stronger evidence will be needed before anyone can conclude that dietary fat increases the risk for breast cancer. Further improvement in dietary methodologies should be useful in clarification of the association between diet and breast cancer.

With regard to the association of replacement estrogens with breast cancer risk, other investigators have also shown a lack of consistency in their findings. They have either observed no association (*42–46*) or found an increased risk for breast cancer with lengthy use of replacement estrogens (*47–50*). Our data do not clearly indicate any association exists between replacement estrogens and breast cancer risk. However, for our long-term users (≥73 mo), we observed a weak suggestion that patients used more estrogens than did neighborhood controls, although the findings were not impressive.

Overall, this study further confirmed that late age at first birth, late age at menopause, early menarche, a family history of breast cancer, and a past history of benign breast disease are risk factors for breast cancer. It did not provide strong support for the hypothesis that a high fat diet or the use of replacement estrogens increases the risk for breast cancer.

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Lung Cancer in Women Living in the Pacific Basin Area [1, 2]

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ABSTRACT—We compared recent incidence rates for lung cancer in females among several regions in the Pacific Basin, Shanghai, Hong Kong, Miyagi, Hawaii, and Los Angeles, by ethnic group using data from the population-based registry in each area. The rates were high among whites and Hawaiians, intermediate in Chinese, and low in Japanese regardless of area. The risk of lung cancer among females who smoke relative to that in female nonsmokers varied from 1 ethnic group to another as did the proportion of smokers in the populations studied. Most of the interethnic differences in lung cancer incidence rates could be explained by differences in smoking patterns. The estimated annual incidence rate for lung cancer in females after subtraction of the proportion of the incidence due to smoking was 7.5/100,000 population in every ethnic group except the Chinese (15-20/100,000 population). Most of the residual incidences of lung cancer were adenocarcinoma of the lung.—Natl Cancer Inst Monogr 69: 197-201, 1985.

Cigarette smoking is well established as the major cause of lung cancer in men. However, among women with lung cancer, many have never smoked cigarettes in their lifetimes (*1, 2*). Because of the variability in incidence rates for lung cancer in the Pacific Basin (*3*), it is important that we determine whether differences in risks for lung cancer can be explained by the different levels of cigarette smoking by persons living in this area.

In this study, we compared the lung cancer incidence rates among women of Chinese, Japanese, Caucasian, and Hawaiian ancestry in the Pacific Basin. We also estimated the proportion of lung cancer among women in these areas that could not be explained by smoking habits, i.e., an estimation of the incidence rates for lung cancer among nonsmoking women.

MATERIALS AND METHODS

Data on all newly diagnosed cases of lung cancer were obtained from the population-based registry of each of the 5 study areas. These data sources and the corresponding years on which the incidence rates were based included: the Shanghai Cancer Registry, 1973–80; the Hong Kong Cancer Registry, 1977–80; the Miyagi Prefectural Cancer Registry for Japan, 1979–80; the Hawaii Tumor Registry, 1976–80; and the University of Southern California/Los Angeles County Cancer Surveillance Program, 1972–77.

Using these incident cases and population data from the census in each area, with adjustments for postcensal changes, we calculated the AAIR by the direct method, standardizing to the World Population (*4*). Because more than 98% of the residents in Hong Kong were Chinese, we used the total incidence rates as representative of rates for Chinese. In Los Angeles County, the rates in whites are those for non-Spanish-surnamed whites.

For 4 of the 5 study areas, RR of lung cancer among women who had smoked at some time were obtained from case–control studies. Only the data for Japan were based on a cohort study. In Shanghai, the proportion of smokers among females was estimated from a cross-sectional study conducted in 1982 covering 55,717 women aged 20 and over (Gao Y-T: Unpublished data). In Hawaii, the proportion of smokers was estimated from a 3% population sample of Japanese, Chinese, Hawaiians, and Caucasian women who were interviewed as part of the Health Surveillance Program of the Hawaii State Department of Health in 1975–77 (*5*). Age-, race-, and sex-matched neighborhood controls were used in the studies conducted in Los Angeles (Wu AH: Unpublished data) and Hong Kong (*6*) for estimations of the proportion of female smokers in these populations. The data for Japanese in Japan were obtained from a large cohort study covering 29 regions, 4 of which were located in Miyagi. All women aged 40 or over in these districts were interviewed in 1965. The risk estimate was based on the mortality experience of 142,857 women after 13 years of follow-up (*7*).

On the basis of estimates of the proportion of smokers from the population samples and assuming that the proportion of smokers among controls in case–control studies

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ABBREVIATIONS: AAIR = age-adjusted incidence rates; RR = relative risk(s); PARP = population attributable risk percent(s).

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TABLE 1.—*Average annual AAIR for lung cancer among women in selected areas and ethnic groups in the Pacific Basin*

Ethnic group	Area	Period	AAIR[a]	Average annual No. of cases
Chinese	Shanghai	1978–80	19.2	695
	Hong Kong	1977–80	23.7	572
	Hawaii	1976–80	23.1	8
	Los Angeles	1972–77	13.6	3
Japanese	Miyagi	1979–80	8.4	120
	Hawaii	1976–80	13.1	24
	Los Angeles	1972–77	9.6	6
Caucasians	Hawaii	1976–80	35.4	38
	Los Angeles	1972–77	22.4	815
Hawaiians	Hawaii	1976–80	34.5	17

[a] Rates are calculated per 100,000 population.

represents the proportion of smokers in the general population, we computed the residual lung cancer rates, i.e., the rates as they would be if the total population were nonsmokers. The residual rate can be expressed as the actual rate divided by a correction factor; the correction factor = 1 + (RR − 1) × proportion of smokers.

RESULTS

Table 1 presents the AAIR for female lung cancer by ethnic group in the 5 selected areas. The rates were highest in whites and Hawaiians and lowest in Japanese. The rates in Japanese were less than one-half those in whites or Hawaiians and these low rates were observed regardless of the place of residence. The rates among Chinese were generally intermediate to those of Japanese and whites or Hawaiians.

Figure 1 illustrates the estimated AAIR for squamous cell carcinoma and adenocarcinoma of the lung. We adjusted the AAIR for these 2 cell types because of the variability in the proportion of lung cancer with unknown histologic type by study area (approximately 40% in Shanghai, 50% in Hong Kong, 25% in Miyagi, 20% in Hawaii, and 30% in Los Angeles). We obtained these adjusted rates by multiplying the observed rate of each cell type by the ratio of the total lung cancer incidence to that of the unknown histologic type. The rates for squamous cell carcinoma were generally high in whites, intermediate in Chinese, and low in Japanese. This pattern in rates was similar to that observed for all lung cancers (table 1). An exception was the high rate of squamous cell carcinoma in Hawaiians compared with other ethnic groups, but this was based on a small number of cases. On the other hand, the rates for adenocarcinoma were about 10/100,000 in Chinese, whites, and Hawaiians and were much lower in Japanese. The AAIR for adenocarcinoma were about two times higher than for squamous cell carcinoma for all but 1 ethnic group; Hawaiian females showed comparable rates for both histologic types.

The RR and 95% confidence intervals for lung cancer among female smokers from recent studies are summarized in table 2. The RR for squamous cell carcinoma were generally higher than those for adenocarcinoma. Only the preliminary results of a case-control study of Japanese women in Osaka showed higher risk estimates for adenocarcinoma compared with squamous cell carcinoma (Fujimoto I, Hanai A: Personal communication). The RR for all histologies combined ranged from 1.3 for Chinese in Shanghai to 10.5 for Hawaiians in Hawaii. The variation in risk estimates was more apparent for squamous cell carcinoma than for adenocarcinoma, but, in some instances, the confidence intervals of the risks were wide.

Table 3 shows that the PARP of smoking for female

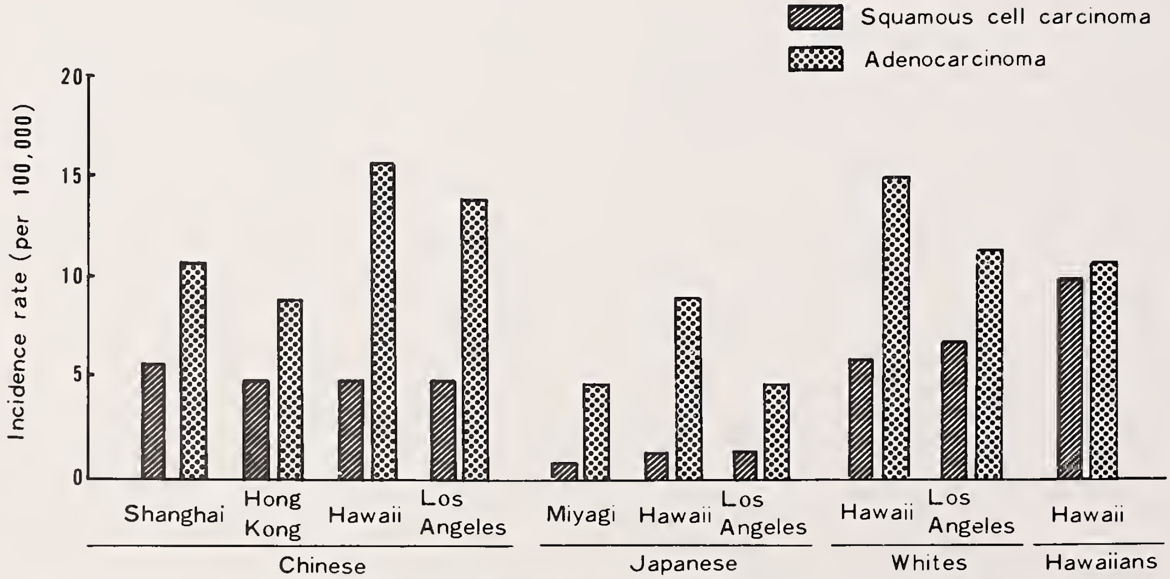

FIGURE 1.—Standardized AAIR for squamous cell carcinoma and adenocarcinoma of the lung among women in the selected areas and ethnic groups in the Pacific Basin. *See* table 1 for the observed period in each area.

TABLE 2.—*The RR and 95% CI for lung cancer among female ever-smokers*[a]

Histologic type	Chinese						Japanese				Caucasians		Hawaiians	
	Shanghai		Hong Kong		Hawaii		Japan[b]		Hawaii		Los Angeles		Hawaii	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Squamous cell carcinoma	2.3	0.5–14.0	3.6	2.0–6.6	11.2[c]	2.4 –52.9	1.4[c]	0.1–16.9	12.7[c]	5.0–32.5	25.2	5.7–111.0	92.4[c]	12.2–700.0
Adenocarcinoma	1.0	0.4– 2.5	1.9	1.1–3.3	.3	0.04– 2.5	3.2[c]	1.0–10.4	4.0	2.3– 6.9	2.9	1.7– 4.9	5.4	2.4– 12.4
All histologies	1.3[d]	0.6– 2.8	2.8	1.9–4.2	1.8	0.7 – 4.8	2.1[e]	0.7– 2.3	4.9	3.2– 7.3	4.4[d]	2.8– 7.0	10.5	6.1– 18.3

[a] CI = confidence intervals.

[b] This is an on-going study in Osaka, Japan.

[c] The RR were calculated for squamous cell carcinoma and small cell carcinoma.

[d] The RR were calculated for squamous cell carcinoma and adenocarcinoma.

[e] The RR is for current daily smokers vs. those who never smoked.

lung cancer differed tremendously by ethnic group. About 80% of the lung cancer in Hawaiian women could be explained by smoking compared with only 10% in Chinese women in Hawaii. The PARP of smoking for squamous cell carcinoma were higher than for adenocarcinoma in all ethnic groups and geographic areas. In contrast, variation was less in the annual residual incidence rates for all cell types combined. With the exception of Chinese, all ethnic groups showed similar residual rates, about 7.5/100,000. The residual rates among Chinese were almost twice that of the other ethnic groups. However, the residual incidence rates by histologic type varied by area and by ethnicity; the rates for adenocarcinoma (4.2–16.6/100,000) were consistently higher than those for squamous cell carcinoma (0.3–2.7/100,000).

The relationship between the RR for lung cancer and the PARP of smoking in the study areas in the Pacific Basin is depicted in figure 2. The width of each bar indicates the proportion of smokers to nonsmokers in the population, and the height of the unshaded bar indicates the residual rate for all cell types combined.

DISCUSSION

The incidence rates for female lung cancer varied among selected areas in the Pacific Basin, but each ethnic group showed similar incidence rates regardless of the area of residence. The interethnic differences in the RR for lung cancer among female smokers residing in the same area suggest that the association between smoking and lung cancer may be confounded by factors specific to ethnicity. The characteristics of smokers, i.e., type and amount of cigarettes smoked, age at starting to smoke, and inhalation pattern, known to be important in the evaluation of the risk of cigarette smoking (*8*), need to be considered because of possible ethnic differences.

The proportion of smokers and the PARP of smoking for lung cancer differed by geographic area and by ethnic group. It is not apparent why the PARP were also different among Chinese and Japanese living in different areas. Differences in the ratio of adenocarcinoma to squamous cell carcinoma (fig. 1) may account for some of the variation because adenocarcinoma is less strongly associated with smoking than is squamous cell carcinoma. In contrast, Caucasian, Japanese, and Hawaiian women had similar residual rates, most of which were adenocarcinomas. Only Chinese women had higher residual rates, regardless of whether they lived in Shanghai, Hong Kong, or Hawaii. Using data from previous studies, we estimated the residual lung cancer rates among Chinese, Japanese, and Caucasian males. The residual rates were 7.6 for Japanese men in Japan (*7*), 5.2 and 9.9, respectively, for Chinese men in Hong Kong (*9*) and in Shanghai (Gao Y-T: Unpublished data), and 10.6 for white men in Los Angeles County (*10*). This analysis of residual rates indicates that nonsmoking Chinese females have higher incidence rates for lung cancer than other female and male nonsmoking populations in the Pacific Basin.

Etiologic factors for lung cancer specific to Chinese women have not been identified. International comparisons are needed to establish the specific host and envi-

TABLE 3.—*The PARP of smoking and residual incidence rates for female lung cancer*

Incidence rates	Chinese			Japanese		Caucasians	Hawaiians
	Shanghai[a]	Hong Kong	Hawaii	Japan	Hawaii	Los Angeles	Hawaii
PARP	4	36	11	13	44	66	79
Residual incidence rates[b, c]	18.4	15.2	20.5	7.5	7.4	7.5	7.3

[a] Subjects were ≥ 40 yr old.

[b] Rates are calculated per 100,000 population.

[c] *See* table 1 for the observed period in each area.

ronmental factors characteristic of this high-risk group, and collaborative studies in Chinese women residing in the different areas in the Pacific Basin should be encouraged.

Several factors have been suggested that explain the similar residual rates in the other ethnic groups. Passive smoking was reported as a risk factor for lung cancer among female nonsmokers in Japan and Greece (*11, 12*), but this was not observed in Hong Kong (*6, 13*). Other types of indoor air pollution should also be considered. Among white females in Los Angeles County, domestic exposure to coal burning was reported to be a risk factor for lung cancer (Wu AH, Henderson BE, Pike MC, et al: Unpublished observations). They also found that women who had pneumonia in their childhood showed an elevated risk for lung cancer. Similarly, Koo reported an association between a history of chronic bronchial irritation and risk for lung cancer among Chinese females in Hong Kong (unpublished data).

Dietary factors may also play an important role in the etiology of lung cancer. An inverse relationship between intake of vitamin A or beta-carotene and risk for lung cancer has been reported (*14*). Results of several recent studies suggested a role for serum cholesterol. Hinds et al. (*15*) reported high intake of cholesterol to be a risk factor for lung cancer in men. Observations from 2 Japanese studies suggested that the role of cholesterol may be especially important for adenocarcinoma. Shimizu (unpublished results) determined that individuals with adenocarcinoma of the lung showed higher serum cholesterol levels adjusted for smoking than those with other cell types of lung cancer at hospital admission for their lung cancer. Moreover, if obesity can be used as a surrogate measure of cholesterol level, patients with adenocarcinoma of the lung also showed higher ratios of weight to height, i.e., an index of obesity (*16*).

Uniformity in the histopathologic classification is required when international comparisons are made. We did not confirm the comparability of the histologic typing of lung cancer in the 5 study areas, but the World Health Organization Classification (*17*) was routinely used in all areas. The results regarding interethnic differences within 1 area are reliable, even if some of the intercountry variability may be attributed to differences in diagnostic practice or classification standards.

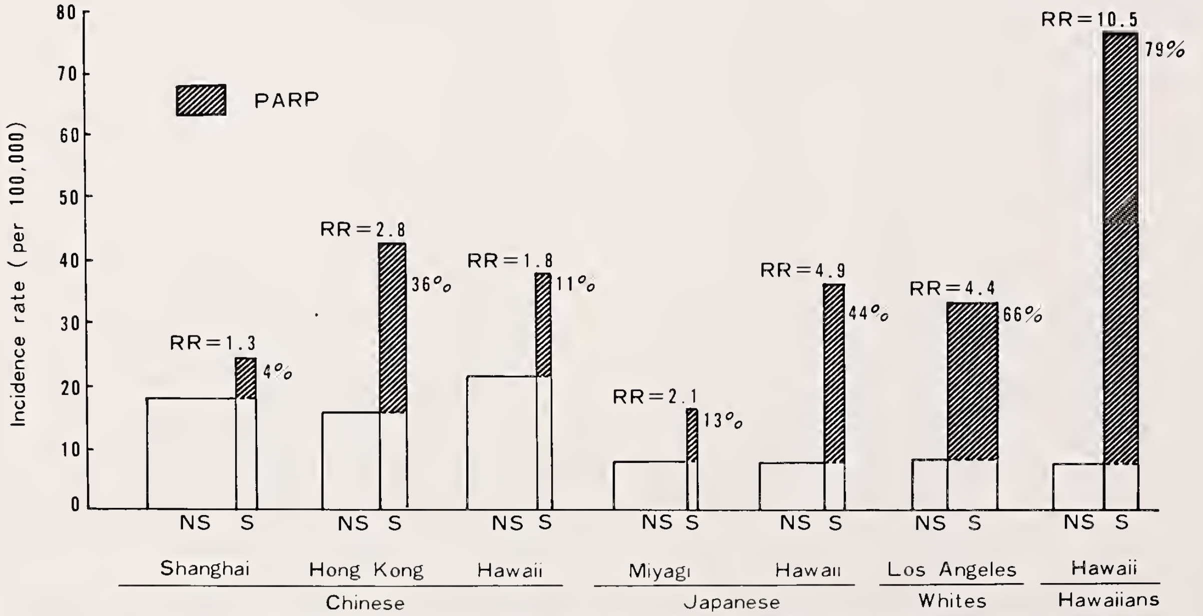

FIGURE 2.—Lung cancer incidence by smoking habit among women in the selected areas and ethnic groups in the Pacific Basin. *See* table 1 for the observed period in each area. NS = nonsmoker; S = smoker.

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Epidemiology of Nasopharyngeal Carcinoma in Malaysia and Hong Kong [1, 2]

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ABSTRACT — We conducted 2 case-control studies with Malaysian and Hong Kong Chinese and investigated the association between salted fish intake and nasopharyngeal carcinoma (NPC). Both studies show a highly significant association between salted fish intake, especially during childhood, and NPC. Furthermore, from our results we estimate that the majority of NPC cases occurring in the southern Chinese can be attributed to their consumption of this food early in life. — Natl Cancer Inst Monogr 69: 203-207, 1985.

Among Chinese living in or originating from the southeastern provinces of China (*1, 2*), NPC is a common cancer. The incidence is especially high in the province of Guangdong; the age-standardized (world population) incidence rates in males are greater than 50/100,000 in certain parts of the Province (*2*). On the other hand, risk of NPC in Chinese outside the high-risk region is only moderately elevated compared with low-risk populations, such as whites in North America and Europe whose age-standardized incidence rates are less than 1/100,000 (*1, 3*). Earlier work on the etiology of NPC in southern Chinese emphasized exposure to carcinogens in smoke or dust. However, findings from these studies suggest that such exposure fails to account for the majority of patients with NPC in this high-risk population (*2, 4, 5*).

Thirteen years ago, Ho (*4, 6*) first suggested that consumption of salted fish, a traditional food of the southern Chinese, might be a risk factor for NPC. Since then, results from epidemiologic and experimental investigations have lent support to such a hypothesis. Salted fish extracts were found to contain volatile nitrosamines (*7-10*) and exhibit mutagenic activity (*11*). Wistar albino rats fed salted fish passed mutagenic urine (*12*), and in an experiment in which 20 Wistar albino rats were fed steamed salted fish, 4 subsequently developed carcinomas in the nasal or paranasal regions, whereas none of the 6 control rats did (*13*). The possible role of salted fish intake in the etiology of NPC has now been investigated in 4 case-control studies in Chinese. In the first 2, a positive association was found between salted fish intake and NPC (*5, 14*). In Los Angeles, significantly more Chinese patients reported current consumption of Cantonese-style salted fish compared with controls [RR for more than once a week consumption compared with none = 3.1; (*5*)]. In Hong Kong, Cantonese-style salted fish was fed to infants during weaning significantly more often in households with a patient with NPC than in control households [RR = 2.6; (*14*)]. We conducted the 2 most recent case-control studies; the findings with the Malaysian Chinese were recently published (*15*). Here we review the findings of the first study and present preliminary results from the second (recently completed), based on the first 200 pairs of case-control interviews.

THE MALAYSIAN STUDY

Because a detailed description of this study has been published (*15*), only a summary of the study methods and results is presented here.

Our patients were drawn from those treated at the Institute for Radiotherapy, Kuala Lumpur General Hospital, the only major center offering radiation treatment for NPC in Malaysia. Only those with histologic confirmation were included in the study. Neighborhood controls were individually matched on race, sex, and age.

All interviews were conducted in the homes of the participants by 2 trained Chinese interviewers using a standard questionnaire. The questionnaire requested information on the use of alcohol, tobacco, nasal ointments; on dietary habits including the consumption of salted fish in childhood and in adolescence; and a complete occupational and medical history.

The case group consisted of 65 males (mean age, 44.8 yr) and 35 females (mean age, 44.7 yr). Eighty-three patients and 86 controls were born in Malaysia. Cases and controls were similar with respect to place of birth, marital status, ethnic subgroup (Cantonese, Hakka, Chiu Chau, Fukien, other), and social class.

A history of salted fish intake in childhood was significantly associated with NPC (RR=3.0; one-sided P=.04), as illustrated in table 1. The RR for daily consumption of this food item in childhood compared with nonconsumption was 17.4, with 95% confidence limits=2.7, 111.1. Most participants maintained the same frequency pattern of salted fish intake during adolescence. All 17 patients and controls who ate salted fish daily in childhood continued to eat this food daily in adolescence. No significant

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ABBREVIATIONS: NPC = nasopharyngeal carcinoma; RR = relative risk(s).

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TABLE 1. *Risk factors for NPC among Malaysian Chinese*

Factor	No. of patients	No. of controls	Matched RR	One-sided *P*
Salted fish intake during childhood				
Ever eaten				
No	5	13	1.0	.04
Yes	87	79	3.0	
Frequency				
Never	5	13	1.0	<.001
<Daily	70	73	2.8	
Daily	14	3	17.4	
Occupational exposure				
Smoke				
No	87	97	1.0	.006
Yes	13	3	6.0	
Dust				
No	48	75	1.0	<.001
Yes	52	25	4.0	
Smoke or dust, or both				
Never	42	74	1.0	<.001
1–9 yr	27	15	3.4	
≥10 yr	31	11	11.4	

TABLE 2. *Use of cigarettes, alcohol, and nasal oils by Malaysian Chinese patients with NPC and controls*

Factor	No. of patients	No. of controls	Matched RR	One-sided *P*
Cigarettes				
Ever smoked	56	51	1.4	.24
No. smoked/day				
None	44	49	1.0	.40
≤9	25	19	1.7	
10–29	23	23	1.2	
≥30	8	9	1.0	
Alcohol consumption				
Rarely	66	67	1.0	.13
≥1/month	4	10	.3	
≥1/week	15	16	.9	
Daily	15	7	2.8	
Use of nasal oils 10 yr ago	19	14	1.5	.22
Use of tiger balm 10 yr ago	44	53	.7	.18

difference was observed between patients and controls in the kinds of salted fish eaten.

The association between NPC and occupational exposure to smoke and dust was statistically significant (RR = 5.0; $P<.001$) as was the dose-response relationship ($P<.001$) with increasing duration of exposure (table 1). This association with dust or smoke exposure was independent of salted fish consumption during childhood.

Patients' and controls' habits were similar in regard to their use of tobacco, alcohol, and nasal oils (table 2).

THE HONG KONG STUDY

Materials and Methods

Incident cases of NPC were identified among Chinese residents of Hong Kong who were under 35 years of age. We restricted our patient population to those under age 35 to obtain better information on childhood diet and other exposures. Eligible patients diagnosed after February 28, 1981, were asked to participate in the study. Of the first 207 contacted, 7 refused to be interviewed. Patients were identified from the files of 4 hospitals (Queen Elizabeth Hospital, Queen Mary Hospital, Hong Kong Sanatorium and Hospital, and Baptist Hospital) which, according to data collected by the Hong Kong Cancer Registry, together identified over 90% of all new cases of NPC in Hong Kong.

We used friends of patients as controls; they were individually matched to the patients on sex and date of birth (within 5 yr). At the end of each interview, we asked the patient to provide us with the name of a close friend (excluding blood relatives) who met the matching criteria. We attempted to interview all mothers of patients and controls who resided in Hong Kong, but 48 mothers of patients either had died or did not reside in Hong Kong; of the 152 contacted, 6 refused to be interviewed. Of the mothers of controls, 23 had died, 40 did not reside in Hong Kong, and 15 refused to be interviewed. In all, we interviewed 146 and 122 mothers of patients and controls, respectively, and 100 matched pairs were interviewed.

All interviews were conducted in person by a trained interviewer using a standard questionnaire for patients and controls and a separate questionnaire for their mothers. The former questionnaire requested information on place of birth; ethnic origin; dietary habits (3 yr ago and at age 10); occupational exposure to smoke, dust, or fumes; exposure to incense, anti-mosquito coils, and other domestic inhalants (3 yr ago and at age 10); cigarette smoking; use of nasal oils; lifetime history on type of cooking fuel used; prior ear or nose disease; and family history of NPC. The questionnaire for mothers contained detailed questions on weaning habits, dietary habits during childhood (between 1 and 2 yr and at age 10); exposure to smoke, dust, or fumes at home; chronic illnesses of

TABLE 3.—*Traditional food items included in the questionnaires for the Hong Kong study*

Food item	Chinese name
Salted foods: fish, pork, vegetables, roots, olive, duck egg	Harm yu, harm ju yoke, mui choi, harm choi, chung choi, choi po, larm gok, harm dann
Cured meats: pork, duck, pork sausage, liver sausage	Laap yoke, laap arp, laap cheung, gone cheung
Dried foods: shrimp, gingko seed, fruits	Ha mei, hung joe, bark guor, chan pai mui, gar ink gee
Sauces and condiments: soy sauce, fish sauce, oyster sauce, shrimp paste, crab paste, bean pastes	See yao, yu lo, ho yao, harm ha, poun kay go, tau si, min si, hoi sin cheung
Cooling soup	Leung char
Moldy bean curd	Fu yu
Fermented duck egg	Pay dann

the ear or nose; and use of nasal oils. Information on diet included frequency of consumption of all preserved foods eaten by southern Chinese. Because cooling soup, a type of medicinal drink, is unique to southern Chinese, we included it in our food list, and we also asked about various sauces and condiment pastes used by Chinese in their cooking (table 3). Other food items were fresh meats and fish, milk, bread, oranges and other fruits, carrots, tomatoes, and fresh leafy green vegetables.

We used the matched-pair methods (*16*) to analyze the interview data. We also analyzed the data on all mothers using methods of cross-classification with sex as the stratifying variable (*16*). Results from the stratified analysis were similar to those from the matched analysis. All data presented in this paper were based on the matched analysis. Pairs in which either the patient or control had a missing value were eliminated from the corresponding analysis.

Results

Our patients numbered 128 males and 72 females, and their mean age at diagnosis was 29.3 years. Controls had a mean age of 28.8 years at date of diagnosis of the index case. One hundred thirty-nine patients (70%) were born in Hong Kong compared with 120 controls (60%). Only 8 patients and 7 controls were born outside of Guangdong Province. Participants were similar with respect to ethnic origin (Cantonese, Sze Yap, Chiu Chau, elsewhere in Guangdong, Fukien/Taiwan, elsewhere in China), marital status, and level of education. The diagnosis of all but 3 patients was confirmed histologically.

Table 4 presents the frequency of salted fish consumption during various periods. Consumption during each of the recorded periods was significantly associated with NPC; the association was especially strong for early childhood. At age 10, the RR for weekly consumption of salted fish compared with less than monthly consumption was 34.4 and the 95% confidence limits equaled 11.7, 101.5. The frequency of salted fish intake at age 10 as estimated by the mother agreed closely with that of the offspring. None of the responses between the mother and her offspring differed by more than one frequency category. Between 1 and 2 years of age, individuals who had salted fish as one of their typical meals (indicated as "often" in table 4) had an RR for NPC of 26.6, with 95% confidence limits = 6.5, 108.9. During weaning, significantly more mothers of patients than those of controls fed salted fish to the subjects (RR = 8.8, 95% confidence limits = 4.2, 19.8). In contrast, the 2 groups of mothers did not differ in their feeding of fresh fish to the subjects (97 and 92% of mothers of patients and controls, respectively).

TABLE 4.—*Frequency of salted fish consumption among patients with NPC and controls during various periods, Hong Kong*[a]

Period	Food item	No. of patients	No. of controls	Matched RR	95% Confidence interval
Three yr ago	Salted fish				
	Rarely	89	127	1.0	
	≥1/mo	75	56	1.9	1.2, 3.0
	≥1/wk	30	16	2.8	1.4, 5.6
	Daily	6	1	7.3	0.9, 62.5
	Salted fish head soup				
	Rarely	181	193	1.0	
	≥1/mo	19	7	3.4	1.2, 9.6
At age 10 yr	Salted fish				
	Rarely	7	88	1.0	
	≥1/mo	105	81	16.1	5.8, 44.5
	≥1/wk	86	29	34.4	11.7, 101.5
	Salted fish head soup				
	Rarely	151	185	1.0	
	≥1/mo	46	12	5.3	2.5, 12.3
Between ages 1 and 2 yr	Salted fish				
	Never	13	68	1.0	
	Sometimes	58	25	8.2	3.5, 19.2
	Often	27	5	26.6	6.5, 108.9
	Salted fish head soup				
	Never	79	96	1.0	
	Ever	18	1	18.0	2.9, 369.9
	Salted fish broth				
	Never	21	73	1.0	
	Sometimes	51	18	6.4	3.0, 14.0
	Often	25	6	11.9	3.6, 39.6
During weaning	Salted fish				
	Never	19	81	1.0	
	Ever	81	19	8.8	4.2, 19.8

[a] Total may not add up to 200 case-control pairs or 100 patient-mother/control-mother pairs due to missing values.

TABLE 5.—*Occupational exposure to smoke, dust, or fumes among patients with NPC and controls, Hong Kong*

Factor	No. of patients	No. of controls	Matched RR	Adjusted RR[a]
Smoke				
Never	193	198	1.0	1.0
Ever	7	2	3.5	3.4
Dust				
Never	144	160	1.0	1.0
Ever	56	40	1.7[b]	1.4
Chemical fumes				
Never	134	156	1.0	1.0
Ever	66	44	2.0[b]	1.1

[a] Adjustment was made for salted fish intake at age 10.

[b] $P < .05$.

As expected, consumption patterns during the different times were highly correlated. A stepwise logistic regression analysis showed that consumption during weaning was most significantly associated with NPC. The second factor to enter the regression equation was consumption at age 10 years. Residual effects of the remaining salted fish variables were not significant. Patients and controls who ate salted fish regularly (at least monthly) 3 years ago were similar to the usual kind of salted fish eaten ("soft" versus "tough" meat) and the usual method of cooking it (over 90% of both groups reported steaming the fish over rice). Besides salted fish, consumption (3 yr ago or during childhood) of a number of preserved foods including fu yu (moldy bean curd), salted pork, salted shrimp, laap yoke (cured meat), pork sausage, liver sausage, mui choi (salted mustard green), dried shrimp, dried red date, cooling soup, chan pai mui, and gar ink gee (dried fruits) were significantly associated with NPC. None of these foods remained significantly associated with NPC after adjustment for salted fish intake.

We found a history of NPC among first-degree relatives to be a significant risk factor for NPC; compared with 3 controls, 16 patients reported such a history. All except 1 of these 16 patients and 1 of 3 controls ate salted fish regularly during childhood.

Our patients were more likely than controls to have been exposed to smoke, dust, or chemical fumes on their jobs (table 5). None of the exposures was statistically significant when adjusted for salted fish intake at age 10 years. Similar results were obtained when we adjusted for salted fish intake both at weaning and at age 10. Our design, of course, limits our ability to study the association with occupational exposure. These young patients had worked only 10–15 years.

There was no difference between patients and controls in their exposure to anti-mosquito coils. However, more patients than controls were exposed to incense (table 6). The RR remained significant after adjustment for salted fish intake at age 10. Similar adjusted RR were obtained when we adjusted for salted fish intake both at weaning and at age 10, even though they were no longer statistically significant. We found no significant difference between patients and controls in their use of various types of cooking fuels.

Furthermore, we found no association between cigarette smoking and NPC. Chronic ear or nose conditions that lasted 6 months or longer were not associated with NPC (table 7). We also compared the occurrence of such conditions before age 15 between patients and controls; again, no association with NPC was observed. Few subjects were exposed to nasal oil at age 10. On the other hand, significantly more patients used nasal oil 3 years ago compared with controls. Reasons given for the use, however, suggest that it was related to the onset of their disease.

TABLE 6.—*Domestic exposure to incense or anti-mosquito coils among patients with NPC and controls, Hong Kong*

Period	Factor	No. of patients	No. of controls	Matched RR	Adjusted RR[a]
Three yr ago	Incense				
	Never	47	65	1.0	1.0
	Ever	153	135	1.6[b]	1.9[b]
	Anti-mosquito coils				
	Never	149	148	1.0	1.0
	Ever	51	52	1.0	1.1
At age 10 yr	Incense				
	Never	28	46	1.0	1.0
	Ever	172	154	2.0[b]	2.7[b]
	Anti-mosquito coils				
	Never	132	134	1.0	1.0
	Ever	68	66	1.1	1.2
At birth	Incense				
	Never	14	19	1.0	1.0
	Ever	86	81	1.7	1.4
	Anti-mosquito coils				
	Never	75	69	1.0	1.0
	Ever	25	31	.6	.6

[a] Adjustment was made for salted fish intake at age 10.

[b] $P < .05$.

TABLE 7.—*Prior ear or nose conditions among patients with NPC and controls, Hong Kong*

Condition	Patients	Controls
Nasal allergy	4	9
Otitis media	2	1
Sinusitis	5	3
Nasal bleeding	1	0
Total	12	13
Before age 15 yr		
Nasal allergy	1	5
Otitis media	2	0
Sinusitis	1	1

DISCUSSION

Our 2 studies clearly demonstrate that consumption of salted fish is a most important risk factor for NPC in Chinese. Our Hong Kong data estimate that at least 80% of NPC occurring in southern Chinese can be attributed to consumption of salted fish before the age of 2. The hypothesis that salted fish intake is an important risk factor for NPC in Chinese is consistent with many aspects of the observed pattern of this disease in Chinese. Salted fish is a favorite food among southern Chinese, especially those in Guangdong Province, but it is rarely eaten by the low-risk northern Chinese. In southern Chinese, NPC displays an inverse relationship with social class (*2*), and salted fish is traditionally one of the cheapest foods available to supplement rice in South China. Because NPC is the most common cancer in southern Chinese 15 to 34 years old (*17*), exposure to the etiologic agent(s) early in life is suggested. Consumption of salted fish early in life would also explain the high rates observed among migrants residing in low-risk areas, such as North America (*2, 18*). The Hong Kong data also imply a maternal link in the transmission of this disease in some families. Eight mothers compared with 1 father had NPC among the 15 patients with a positive family history and who were exposed to salted fish during childhood. This finding indicates that the mothers of patients were feeding the children in the same way their mothers fed them, thereby passing the disease on to the next generation.

The limited experimental data suggest that preformed nitrosamines contained in the salted fish may be the causative chemical agent(s) (*7–10*). More data are needed for substantiation of this claim. Because this Cantonese-style salted fish is the first food that has been shown to be a probable cause of a human cancer, we urge that intense laboratory investigations be made to further our understanding of the chemical agents involved and the possible mechanisms of carcinogenesis.

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Attempts to Isolate N-Nitroso Compounds From Chinese-style Salted Fish [1, 2]

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ABSTRACT—Various types of salted fish have been collected from Hong Kong and analyzed for volatile nitrosamines and bacterial mutagenicity. Both of these parameters were low in the samples as collected. Exposure of these samples to nitrite yields substantial quantities of nitrosamines and mutagenic activity.—Natl Cancer Inst Monogr 69: 209-211, 1985.

Salted fish has been shown to be a highly significant risk factor for NPC in 2 case-control studies conducted in Malaysian and Hong Kong Chinese (*1*). The original suggestion that salted fish intake might be a risk factor for NPC was presented by Ho (*2*), and the background and discussion of earlier works are presented in the paper describing the 2 case-control studies (*1*).

To examine the hypothesis (*3*) that nitrosamines in salted fish were the putative carcinogens for NPC, we examined samples of salted fish collected in Hong Kong for preformed volatile nitrosamines. We also decided to determine whether nitrosatable precursors for formation of mutagens could be found in these fish samples. Earlier results had shown fava beans (*4*) and a Japanese fish to be mutagenic after such treatment (*5*), and additionally nitrosated fish has been shown to induce gastric cancer in the rat (*6*).

MATERIALS AND METHODS

Collection of fish samples.—Nine samples of salted fish of eight types were purchased in a market in Hong Kong. Two were samples of yellow croaker and 1 each of mackerel, anchovy, croaker, red snapper, black pomfret, and white croaker. One sample was imported from Japan of unknown type. Of the 8 samples of salted fish processed in Hong Kong, the 4 of white croaker, black pomfret, red snapper, and mackerel were of the "muihurn" type [*see* Appendix for explanation (*7*)].

Analysis for bacterial mutagens.—Ten grams of each fish sample were blended in a Hamilton Beach Food Processor and put into a 125-ml Erlenmeyer flask; then we added 10 ml water containing 0.281 g sodium chloride and 10 ml containing 0.069 g sodium nitrite and mixed them; the pH was adjusted to 3 with concentrated hydrochloric acid. The flask was wrapped in aluminum foil and held at room temperature for 1 hour. (All subsequent steps were performed in subdued light.) After 1 hour, 10 ml water containing 0.11 g ammonium sulfamate was added to the fish slurry to quench the reaction. This mixture was then cooled to 4° C in ice, was extracted twice with 50-ml aliquots of cold hexane, then twice with 50 ml of a 9:1 dichloromethane–methanol mixture. This latter fraction was then concentrated to approximately 10 ml with the use of a Kuderna-Danish, then taken down the final few milliliters with a stream of nitrogen. Fifty microliters dimethyl sulfoxide was added to the sample before concentrating the last 0.5 ml. The samples were capped, wrapped in foil, and frozen at −80° C until we analyzed them for mutagens using *Salmonella typhimurium* TM 677 (*4*).

Analysis for volatile nitrosamines.—Twenty-five grams of each fish sample was cut into minute pieces and added to 50 ml Nujol (mineral oil) in a vacuum distillation apparatus. The vacuum pressure was gradually decreased until the Nujol stopped frothing. Heat was gradually applied with a Variac until the temperature reached about 120° C in the sample vessel. The vacuum pressure at this time was about 1.5 to 2.0 torr. After cooling down, the trap and fittings were washed with about 50 ml distilled water, and the distillate was then extracted with a 3 × 75 ml dichloromethane, dried with magnesium sulfate (anhydrous), and then evaporated on a Kuderna-Danish at 60° C to about 10 ml. We then concentrated this down to 0.5 ml with a stream of nitrogen and analyzed it for volatile nitrosamines using gas chromatography with the Thermal Energy Analyzer, a nitrosamine-specific detector.

RESULTS

Results of the 9 samples of salted fish bought in Hong Kong are reported in table 1. Only trace quantities of dimethylnitrosamine and no other volatile nitrosamines could be found prior to nitrosation. Over one-half of this batch gave strong positive mutagenic responses following

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ABBREVIATION: NPC = nasopharyngeal carcinoma.

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TABLE 1.—*Analysis of salted fish purchased in Hong Kong*[a]

Type of fish	Dilution in forward assay	Background mutant fraction	Nitrosated fish mutant fraction	Nonnitrosated fish mutant fraction	Dimethylnitrosamine, ppb
Imported from Japan	Undiluted	8.0	60.8		2.8
	"	20.3		28.2	
Yellow croaker	1:1	20.9	44.9		NP
	Undiluted	20.3		19.9	
Yellow croaker	"	20.9	24.7		0.64
	"	20.3		18.6	
Mackerel	1:2	20.9	219.1		ND
	1:1	20.3		27.8	
Anchovy	1:1	20.9	37.4		NP
	Undiluted	20.3		28.4	
Croaker	"	20.9	37.1		2.0
	"	20.3		25.4	
Red snapper	"	20.9	124.9		ND
	"	20.3		18.1	
Black pomfret	"	20.9	115.4		"
	"	20.3		19.9	
White croaker	1.2	20.9	78.6		"
	Undiluted	20.3		20.6	

[a] Underlined values indicate a highly significant ($P = .01$) effect of nitrosation; mutant fraction = mutants/survivor × 10^5. NP = not performed; ND = none detected.

nitrosation. We have made no attempt to characterize the N-nitroso compounds formed as a result of nitrosation.

DISCUSSION

Of the salted fish samples we examined, none had significant levels of volatile nitrosamines. Similarly low levels (sub-parts per million) of dimethylnitrosamine in salted fish have been reported by Fong and Chan (*8*) and by Huang et al. (*9, 10*). These levels are comparable to those detected in cured meats consumed in Europe and do not seem sufficient to explain the high risk of NPC associated with the consumption of Chinese salted fish.

On the other hand, some of the samples gave a highly significant mutagenic response following nitrosation, and our experience with similar material suggests that nitrosation also induces the formation of substantial quantities of volatile nitrosamines. The absence of nitrosamines and mutagenic substances in the untreated fish and the potential for formation after exposure to nitrite indicates one avenue for further research. Precursors of N-nitroso compounds may react with exogenous (or endogenous) sources of nitrite (or nitrate) to form significant amounts of nasopharyngeal carcinogens. Alternatively, salted fish may contain other types of carcinogenic substances which have not been identified. A systematic search for such substances is under way.

APPENDIX

Generally, during processing of salted fish in South China (*7*) the fish is not gutted prior to salting. Occasionally when bigger fish such as red snapper are salted, the guts are drawn out through the throat, without making an incision in the belly of the fish. Salting is done in wooded vats, and the fish are arranged in alternate layers with coarse rock salt. In a few days, the fish will be immersed in brine, and weights are placed on the surface (often large stones placed on top of grass mats) to prevent the fish from floating. Length of salting time ranges from 1 to 5 days, after which the fish are taken out to dry in direct sunlight. The fish are usually spread out on woven grass mats. They are turned every few hours and left out as long as sunlight is available. The time of drying is 1 to 7 days, depending on the size of the fish and the weather. During drying, insect infestation can be a serious problem, especially in damp weather. Unfortunately in South China, relative humidity is over 80% about 8 months of the year, and it is not unusual to reach 96–99% during the summer months. Sometimes, the fish is allowed to soften by decomposition before salting. This produces the "muihurn" salted fish; the rest are called "sud yoke" (literally, tough meat) salted fish.

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Hepatitis B Virus and Primary Liver Cancer on Chongming Island, People's Republic of China [1]

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ABSTRACT—Data on potential risk factors for primary liver cancer (PLC), including hepatitis B virus (HBV) infection, contaminated drinking water, maize consumption, and use of tobacco and alcohol were collected from 12,222 males over 40 years of age living on Chongming Island, a high-risk area for PLC. During the first 3 years of follow-up (1980–82), 70 deaths from this disease occurred among study subjects. Preliminary results indicate that HBV carriers were 6.7 times more likely to die of PLC than were noncarriers ($P<.05$). No association was found between PLC and alcohol consumption. More data are needed for evaluation of the relationships between cigarette smoking, maize consumption, contaminated drinking water, and PLC on Chongming Island. — Natl Cancer Inst Monogr 69: 213–215, 1985.

In China, PLC ranks third among all cancers and causes 100,000 deaths per year. High mortality areas are concentrated in the southeastern coastal region, including many coastal islands (*1*). Chongming Island is one such island with one of the highest mortality rates of PLC in China. The adjusted (world population) mortality rate of PLC in 1974–78 was 50.8/100,000 in males and 17.0 in females (*2*). The island is situated at the outlet of the Yangtze (Changjiang) River. Seven hundred and fifty thousand residents live on this island; over 85% are local-born peasants. The PLC rates were higher in the eastern than the western part of the island, higher in rural areas than in towns (*2*), and seem to be gradually decreasing in recent years (*3*).

We initiated a prospective cohort study on Chongming Island in November 1979 to investigate the HBV infection, exposure to aflatoxin and contaminated water, and use of tobacco and alcohol in the etiology of PLC. Preliminary results from the first 3 years (1980–82) of follow-up are presented.

MATERIALS AND METHODS

All male residents over 40 years of age in 4 communes on Chongming were considered potential study subjects. Two of these communes were located in the eastern part and the other 2 in the western part of the island; 12,222 men (98% of all eligible subjects) participated in the study.

We collected serum samples from each man to test for various HBV markers. The HB surface antigen was tested by the method of reverse passive hemagglutination, anti-HB surface antigen by passive hemagglutination, and the anti-HB core antigen by immune adherence hemagglutination. Subjects who were either positive for the surface antigen or positive for the anti-HB core antigen in the absence of anti-HB surface antigen were considered HBV carriers.

Data on lifetime sources of drinking water, smoking and drinking habits, and maize consumption were collected by trained barefoot doctors using a standard questionnaire.

Deaths from PLC were ascertained through the Chongming Anti-Epidemic Station. Data on all PLC cases were reviewed by Dr. Gao at the end of each follow-up year.

We stratified the men on the basis of their age group, HBV status (carrier or not), and exposure history of the risk factor(s) under study and computed the PLC mortality rate within each stratum by using cumulative person-years as the denominator. The age distribution of all subjects was used as a standard for calculating age-adjusted rates. We determined differences between rates by the chi-square test (*4*).

RESULTS

In the first 3 years of follow-up, 70 men died from PLC. Fifty-seven (81.4%) of these patients were positive for alpha-fetoprotein with a level of 500 ng or higher. Of the 12,222 subjects, 1,971 (16.1%) were HBV carriers, and 37 of the 70 deaths occurred among HBV carriers. The age-adjusted mortality rate of PLC in HBV carriers was 650.9/100,000 person-years, 6.7 times higher than the rate in noncarriers, which was 98.6/100,000 person-years. The difference was statistically significant.

The study participants had five main sources of drinking water: house ditch, field ditch, field well, kitchen well, and river. Since 1964, the County Health Bureau initiated 2 programs aimed at improving the quality of drinking

ABBREVIATIONS: PLC = primary liver cancer; HBV = hepatitis B virus; AFB_1 = aflatoxin B_1.

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TABLE 1.—*Percentage of study subjects using the various kinds of drinking water in 1949 and 1979*

Water source	1949	1979
House ditch	33.6	7.0
Field ditch	26.9	8.3
Field well	6.3	42.4
Kitchen well	0.2	18.6
River	28.0	19.3
Other	5.0	4.4
Total	100.0	100.0

water that resulted in a change for the better in water supply for close to 60% of our subjects. Table 1 shows the proportion of men who used the various kinds of water for drinking in 1949 and in 1979. Considerably fewer subjects relied on house or field ditches for drinking water in 1979 than in 1949, and even fewer used kitchen wells as the main source of drinking water in 1949. Only 5,004 (40.9%) of all the men used the same type of water supply during the last 30 years. The analysis of drinking water supply and PLC was restricted to this group of 5,004 participants who were stratified according to their source of drinking water (except kitchen well). The age-adjusted mortality rate of PLC within each stratum was computed (table 2). In both the HBV carrier and the noncarrier groups, subjects who used river water had the lowest rate of PLC.

The age-adjusted mortality rates of PLC by cigarette smoking status is given in table 3. Subjects who smoked occasionally were excluded from the analysis. The mortality rate among heavy current smokers (≥20 cigarettes/day) was significantly higher than among nonsmokers in the HBV-carrier group; furthermore, as the amount of cigarettes smoked increased, so did the trend in rates. The difference in rates between smokers and nonsmokers who were not HBV carriers was not significant.

One of the aims of our cohort study was to investigate the association between AFB_1 consumption and PLC. Reports from Guangxi Autonomous Region, a high-risk area for PLC in China, indicated that maize was more likely to be contaminated by AFB_1 than were wheat and rice (*5*). Maize was one of the staple foods on Chongming Island. In 1981–82, we collected 756 samples of the different kinds of cooked staple food and examined them for AFB_1 contamination. Results showed that AFB_1 contamination was threefold and fivefold higher in maize than that in wheat and rice, respectively (Xu GX: Unpublished observations). Thus we took the amount of maize consumed as a crude measure of AFB_1 ingested.

The amount of maize consumed (as a percentage of all staple foods) in 4 years (1949, 1958, 1967, and 1979) was recorded for each subject. The data in table 4 indicate that maize consumption has been decreasing over the years. Subjects who did not eat it between 1949 and 1979 were considered noneaters. The "ever-consumers" were classified into low (0–24% of all staple foods), moderate (25–50%), and high (50+%) consumption groups according to their eating patterns in 1979. Among HBV carriers, the rate of PLC rose with increasing consumption of maize, but the rates were unstable due to the low cumulative person-years involved (table 5). Among noncarriers, mortality rates of PLC differed little between noneaters of maize and those whose consumption in 1979 constituted up to 24% of all staple foods. No PLC death occurred among noncarriers whose maize consumption made up 25% or more of all staple foods in 1979.

Residents of Chongming prefer to drink a kind of locally made rice wine. The mortality rate of PLC in current drinkers (199.3) was similar to that in nondrinkers (195.4), both among HBV carriers (675.6 vs. 623.5) and noncarriers (96.6 vs. 96.4).

TABLE 2.—*Adjusted mortality rates of PLC in groups with different drinking water supply*

Water source	HBV carrier			Noncarrier		
	Total person-years	No. of deaths	Rate	Total person-years	No. of deaths	Rate
House ditch	381.5	6	1,020.4	1,945.0	3	149.5
Field ditch	563.0	2	390.5	2,114.5	2	89.6
Field well	334.0	7	1,818.3	1,748.0	1	51.9
River	1,236.0	4	340.8	5,083.0	1	18.2

TABLE 3.—*Adjusted mortality rates of PLC among smokers and nonsmokers*

Smoking habit	HBV carrier			Noncarrier		
	Total person-years	No. of deaths	Rate	Total person-years	No. of deaths	Rate
Nonsmoker	1,134.5	4	332.8	5,707.5	7	115.1
Current smoker	3,590.5	26	737.9	17,361.5	17	99.9
≤19 cigarettes/day	3,235.0	21	660.1	15,645.0	15	96.3
≥20 cigarettes/day	355.5	5	1,519.0[a]	1,716.5	2	145.2

[a] Value is significantly higher than that of the nonsmoker group, $P<.05$.

TABLE 4.—*Percent distribution of maize consumption in study subjects*

Maize as percentage of all staple foods	1949	1958	1967	1979
0	9.0	10.4	10.7	16.0
≤25	31.3	36.5	49.7	74.4
25-50	27.1	30.6	35.3	7.9
≥50	32.6	22.5	4.3	1.7
Total	100.0	100.0	100.0	100.0

DISCUSSION

The association of PLC with HBV infection has been reported in many populations (*6*). Our data are consistent with other recent case-control and cohort studies conducted in Chinese populations, all of which show HBV infection to be an important risk factor for PLC in Chinese (*7, 10*).

Su (*11*) suggested that hepatocarcinogenic substances are found in stagnant waters, especially ditch water in Qidong and Haimen Counties (adjacent to Chongming Island). He (*11*) observed a reduction in PLC mortality within 5 years of improving the quality of water supplies in those areas. Preliminary results from our first 3 years of follow-up show that PLC mortality was higher in residents using field well, house ditch, or field ditch water than those using the cleaner river water. However, results for the 3 groups of men who drank dirty water of varying degrees (house or field ditch or field well) are not consistent between HBV carriers and noncarriers. Furthermore, mortality rates computed for the 4 groups with different water supplies were unstable due to the small number of cases and cumulative person-years involved. More data are needed for an evaluation of Su's suggestion that hepatocarcinogenic substances are in the stagnant water in high-risk PLC areas in China.

Results from previous case-control studies suggested that cigarette smoking is an independent risk factor for PLC (*10, 12, 13*). In our prospective study, among noncarriers of HBV the adjusted mortality rate of PLC in nonsmokers was not significantly different from that of current smokers. On the other hand, among HBV carriers the rate in current smokers was higher than in nonsmokers, and the rates increased with the amount of cigarettes smoked per day. Whether cigarette smoking is a co-factor in the etiology of PLC needs further investigation.

No difference in rates was found between current alcohol drinkers and nondrinkers. Our results on the relationship between PLC and maize consumption in this study were difficult to interpret; we need more follow-up data.

TABLE 5.—*Adjusted mortality rate of PLC by level of maize consumption*

Maize as percentage of all staple foods	HBV carrier			Noncarrier		
	Total person-years	No. of deaths	Rate	Total person-years	No. of deaths	Rate
Noneater	589.5	2	272.9	2,314.5	2	99.8
<25	4,230.5	27	640.8	20,691.5	21	104.8
25-50	341.0	4	1,333.4	2,392.0	0	0.0
≥50	99.5	1	1,177.4	456.0	0	0.0

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Relation of Analgesic Use to Renal Cancer: Population-based Findings [1]

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ABSTRACT—A population-based case-control study of renal cancer (495 cases of renal cell cancer, 74 cases of renal pelvis cancer, and 697 controls) was conducted in the Minneapolis-St. Paul 7-county metropolitan area. Information was obtained on a large number of variables, including the use of analgesic drugs. Long-term use (>36 mo) of phenacetin-containing products was associated in both sexes with a twofold increased risk for renal cell cancer. Long-term use of phenacetin- and acetaminophen-containing products was associated with elevated risks of nearly threefold to eightfold for cancer of the renal pelvis. The separate effects of these analgesics could not be adequately assessed because most long-term users took both products.—Natl Cancer Inst Monogr 69: 217-222, 1985.

Cancer of the renal pelvis has been associated with the abuse of analgesic drugs, particularly mixtures containing phenacetin (*1*). The evidence comes from case reports of cancer among analgesic abusers, follow-up surveys of patients with interstitial nephritis or analgesic nephropathy, and recent case-control studies in Australia and the U.S. (*1-7*). Our recent case-control study of renal cell carcinoma in the U.S. (*8*) also indicated an association with phenacetin-containing drugs. However in many of the studies, little information has been given on the use of other types of analgesics. Here we present detailed findings on analgesic use as a possible risk factor from a large, population-based case-control study of renal pelvis cancer (*7*) and renal cell cancer (*8*). The study was conducted in the Minneapolis-St. Paul 7-county SMSA, a part of the U.S. where incidence and mortality rates for renal cancer are unusually high (*9*).

MATERIALS AND METHODS

Cases of renal cell cancer [ICD, 189.0; (*10*)] and renal pelvis cancer (ICD, 189.1) diagnosed in SMSA area residents between January 1, 1974 and June 30, 1979, were identified by a review of the records of area hospitals and the Mayo Clinic that resulted in almost complete ascertainment for the period of the study. A total of 506 cases of renal cell cancer and 78 cases of renal pelvis cancer was ascertained. Cases were restricted to whites due to the small number of nonwhites in the older age groups in the metropolitan area.

We selected controls 30 to 64 years of age using an age- and sex-stratified random sample of all telephone subscribers in the SMSA. Of the households in the SMSA, 98% have telephones (*11*). Controls 65 to 85 years of age were selected with an age- and sex-stratified systematic sample provided by the Health Care Financing Administration of the Social Security Administration. It is estimated that 95% of the individuals 65 years of age and older in the U.S. are in the Health Care Financing Administration record system (*12*).

Patients and controls were identified in 1979 and interviewed in 1980. Due to the retrospective case ascertainment and the case fatality rate for kidney cancer, 237 renal cell cancer and 37 renal pelvis cancer patients were deceased and 14 with renal cell cancer were too ill to be interviewed. The next of kin of these individuals were interviewed. A comparison of the drug histories of patients interviewed directly with those provided by the next of kin of the deceased or severely ill revealed no major differences and are, therefore, combined in the analysis.

A detailed 38-page questionnaire was administered by trained interviewers unaware of the case or control status of the respondents. The items in the questionnaire covered demographic and ethnic variables: use of tobacco and beverage consumption; diet; drug use; and medical, occupational, and residential histories. Exposures after 1973 were excluded from analysis. Eighty-six percent of the interviews were conducted in the respondent's home, and 14% by telephone for those who moved out of the study area or could not be interviewed at home.

Use of the following analgesic drugs (which were listed on a hand card and given to the study subject) were ascertained in the interview: aspirin, APC (aspirin, phenacetin, caffeine tablets or "a perfect cure"), Darvon, Anacin, Tylenol, Bufferin, Empirin Compound, Bromo Seltzer, Alka-Seltzer, Excedrin, Ascriptin, Aspirin Compound, Sinutab, Vanquish, Midrin, Synalogg, Valadol, APAP-(SK-APAP), Contact, Arthralgen, Norgesic, Fiorinal, Repan, Tempra, Medache, BC Tablets, Bancaps, Dristan, and Wigrane. Information was also sought for pain relievers not on the hand card. The screening question asked about consumption of any of these drugs ten times or more during adulthood. If a response for a particular drug was positive, information was sought on the usual frequency of consumption (measured in days per month). If the response was 15 or more days per month, information was sought on the length of time for this level of consumption. If the subject usually consumed the drug fewer

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ABBREVIATIONS: SMSA = standard metropolitan statistical area; OR = odds ratio(s); CI = confidence interval.

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TABLE 1.—*Distribution of renal cell cancer patients and controls by type of analgesic product used*

Analgesic product used	Male				Female			
	No. of patients	Percent	No. of controls	Percent	No. of patients	Percent	No. of controls	Percent
None	50	16	47	11	17	9	35	13
Aspirin only	121	38	150	35	45	25	93	35
Acetaminophen only	3	1	4	1	1	0.5	3	1
Phenacetin only	12	4	12	3	5	3	10	4
Aspirin and acetaminophen	14	5	31	7	11	6	16	6
Aspirin and phenacetin	47	15	83	18	55	30	57	21
Acetaminophen and phenacetin	4	1	3	2	1	0.5	6	2
All 3	62	20	98	23	47	26	49	18
Total	313	100	428	100	182	100	269	100

than 15 days per month, he or she was asked whether it was consumed 15 or more days per month during any particular periods. If the response was positive, information on the length of these periods was sought. Beginning and ending dates for consumption of drugs were not obtained in the interview.

The drugs listed on the hand card were chosen from marketing information on the top 20 prescription drugs and the top 20 over-the-counter drugs purchased in the early 1960s and 1970s in the Minneapolis-St. Paul area. We also reviewed the *Physicians' Desk Reference* from 1955 to 1974 to identify phenacetin-containing drugs and other compound analgesics.

The association between cancer and analgesic use was measured by the OR, an estimate of the relative risk (*13*). To assess confounding, we calculated summary OR using the maximum likelihood method with CI derived from Gant's modification of Cornfield's method (*14*). The test for linear trend (two-tailed) was the Mantel extension of the Mantel-Haenszel procedure (*15*). All OR presented in this paper are adjusted for age and for cigarette smoking, which was found to be a risk factor in earlier analyses (*7, 8*). Initially, the results for female renal cell cancer were adjusted for weight because elevated weight was found to be a risk factor among women, but such adjustment had little effect on the OR and will not be presented. The same control series was used in the analyses of both cancers.

RESULTS

Renal Cell Cancer

Interviews were obtained for 495 patients of the 506 with ascertained renal cell cancer for a response rate of 98%. A response rate of 94% was achieved for population controls 30 to 64 years of age, which was a product of a 97% response rate at both the telephone screening and interview phases. Ninety-eight percent of the controls 65 to 85 years of age were interviewed. Thus of the 714 identified controls, 697 were interviewed.

TABLE 2.—*The OR for renal cell cancer associated with use of phenacetin- and acetaminophen-containing analgesics*[a]

Product	Use	Male				Female			
		Patients	Controls	OR	95% CI	Patients	Controls	OR	95% CI
Phenacetin containing	Never	188	232	1.0	—	74	147	1.0	—
	Ever	125	196	0.7	0.5– 1.0	108	122	1.7	1.1–2.7
	Irregular	99	175	0.7	0.5– 0.9	86	100	1.7	1.1–2.6
	Regular, ≤36 mo	18	17	1.3	0.6– 2.7	10	12	1.9	0.7–5.6
	Regular, >36 mo	8	4	2.2	0.6– 8.9	12	10	2.4	0.8–6.7
								P for trend <.05	
Acetaminophen containing	Never	230	292	1.0	—	122	195	1.0	—
	Ever	83	136	0.7	0.5– 1.0	60	74	1.2	0.8–1.9
	Irregular	70	127	0.7	0.5– 1.0	53	58	1.4	0.8–2.2
	Regular, ≤36 mo	10	4	3.1	0.9–11.8	2	8	0.4	0.1–2.8
	Regular, >36 mo	3	5	0.7	0.1– 3.4	5	8	1.2	0.3–4.6

[a] The OR were adjusted for age and cigarette smoking.

TABLE 3.—*The OR for renal cell cancer associated with use of aspirin products*[a]

Use	Male				Female			
	Patients	Controls	OR	95% CI	Patients	Controls	OR	95% CI
Never	69	66	1.0	—	24	54	1.0	—
Ever	244	362	0.6	0.4–0.9	158	215	1.6	0.9–2.8
Irregular	202	310	0.6	0.4–0.9	130	175	1.6	0.9–2.9
Regular, ≤36 mo	25	24	1.1	0.5–2.2	8	16	1.2	0.4–4.0
Regular, >36 mo	17	28	0.5	0.2–1.0	20	24	1.8	0.7–4.1

[a] *See* footnote *a*, table 2.

Tissue diagnoses were obtained for 460 (93%) of the renal cell cancer cases and 35 (7%) were diagnosed by x ray. Forty-eight percent of the tumors involved the right kidney and 48% the left, with 2% bilateral. The mean age at diagnosis was 62 years for males and 66 for females. Of the 495 patients with renal cell cancer, 313 were male and 182 were female; their controls numbered 428 male and 269 female.

Each analgesic drug assessed in the interview was evaluated separately for an association with renal cell cancer. Although use of no drug was found to be significantly elevated in both sexes, use of Bufferin among women was associated with a significantly increased age- and smoking-adjusted risk (OR = 1.7; 95% CI = 1.1–2.7). The analgesic drugs were divided into 3 groups: acetaminophen-containing, phenacetin-containing, and aspirin products. These groups were developed after a review of the ingredients of the individual drugs for the period 1955 to 1974 (*16–18*). Thus a drug was considered to be phenacetin-containing if phenacetin was included in the formulation at any time from 1955 to 1974. The same procedure was used for categorization of acetaminophen-containing drugs. Aspirin products contained aspirin as the only analgesic ingredient.

The distribution of patients and controls by type of analgesic product used during adulthood is shown in table 1. The most commonly used product by both sexes was aspirin followed by users of all 3 products combined. Among men and women, few were exclusive lifetime users of acetaminophen or phenacetin products. No major case-control differences were observed among males for type of analgesic used. Among females, fewer patients than controls used no analgesics or aspirin only, whereas more patients than controls consumed aspirin and phenacetin products or all 3 products combined, although none of these differences were statistically significant.

Table 2 presents OR associated with the use of phenacetin-containing drugs. Long-term use (>36 mo) was associated with an increased risk for both sexes. The positive trend among women was statistically significant. Use of acetaminophen-containing analgesics was not associated with a clear trend in either sex (table 2). Control for use of phenacetin-containing drugs made little difference in the results. Consumption of aspirin products (table 3) was associated among males with decreased risk ratios, but among women, all risk ratios were elevated, although no particular trend was evident. Control for use of phenacetin-containing drugs did not appreciably affect the risk ratios. However, the risk among women who used aspirin exclusively (45 patients and 93 controls, *see* table 1) was approximately unity (OR = 1.1, 95% CI = 0.5–2.30; OR was adjusted for age and cigarette smoking). Among long-term (>36 mo) aspirin-only users (3 patients and 8 controls), the risk was less than unity (OR = 0.7; 95% CI = 0.1–4.1).

Renal Pelvis Cancer

Interviews were obtained for 74 patients of the 78 with ascertained renal pelvis cancer for a response rate of 95%. Tissue diagnoses were obtained on 73, and all but 3 were

TABLE 4.—*Distribution of patients with renal pelvis cancer and controls by type of analgesic product used*

Type of product	Male				Female			
	No. of patients	Percent	No. of controls	Percent	No. of patients	Percent	No. of controls	Percent
None	2	4	47	11	3	12	35	13
Aspirin only	21	42	150	35	6	25	93	35
Acetaminophen only	0	0	4	1	2	8	3	1
Phenacetin only	2	4	12	3	0	0	10	4
Aspirin and acetaminophen	1	2	31	7	1	4	16	6
Aspirin and phenacetin	8	16	83	18	4	17	57	21
Phenacetin and acetaminophen	3	6	3	2	3	13	6	2
All 3	13	26	98	23	5	21	49	18
Total	50	100	428	100	24	100	269	100

TABLE 5.—*The OR for renal pelvis cancer associated with use of phenacetin- and acetaminophen-containing analgesics*[a]

Product	Use	Male				Female			
		Patients	Controls	OR	95% CI	Patients	Controls	OR	95% CI
Phenacetin containing	Never	24	232	1.0	—	12	147	1.0	—
	Ever	26	196	1.2	0.6– 2.4	12	122	1.3	0.5– 3.4
	Irregular	21	175	1.1	0.6– 2.3	9	100	1.1	0.4– 3.2
	Regular, ≤36 mo	1	17	0.5	0.02–3.9	1	12	1.8	0.4–22.0
	Regular, >36 mo	4	4	8.1	1.2–62.2	2	10	4.2	0.4–42.0
Acetaminophen containing	Never	33	292	1.0	—	13	195	1.0	—
	Ever	17	136	1.2	0.6– 2.5	11	74	2.2	0.8– 5.8
	Irregular	13	127	1.0	0.5– 2.2	7	58	1.8	0.6– 5.4
	Regular, ≤36 mo	2	4	4.7	0.5–43.7	1	8	2.4	0.1–35.6
	Regular, >36 mo	2	5	2.5	0.3–17.7	3	8	5.8	0.8–40.0 *P* for trend <.05

[a] *See* footnote *a*, table 2.

transitional cell tumors. The mean age at diagnosis was 65 years for the 50 males and 67 for the 24 females.

No significant case–control differences were observed for the use of any of the 29 drugs assessed in the interviews. The distribution of patients and controls by type of analgesic product is shown in table 4. Few patients or controls had taken phenacetin or acetaminophen products exclusively.

Long-term use of phenacetin-containing drugs was associated with a significant eightfold increase in risk among males and a fourfold increase in risk among women (table 5). Long-term use of acetaminophen-containing drugs was also associated with an elevated risk in both sexes, with the positive trend being statistically significant among women (table 5). However, the number of patients taking these drugs long term was small, and many of them were long-term users of both analgesic products (table 6). One patient was a long-term user of acetaminophen-containing but not phenacetin-containing products, another was a long-term user of phenacetin-containing but not acetaminophen-containing analgesics, and 4 patients were long-term users of both products.

Use of aspirin products was not associated with a clear trend in risk, except for a slight increase in risk among long-term male users, balanced by a deficit in risk among women (table 7). Among exclusive users of aspirin products (table 4), a larger proportion were male patients than controls (OR = 3.5; 95% CI = 0.7–23.5 adjusted for age and cigarette smoking), whereas among female users, the proportion of aspirin-only users was smaller (OR = 0.8; 95% CI = 0.1–5.7). Among exclusive long-term users of aspirin, 2 were male patients and 12 were controls (OR = 2.7; 95% CI = 0.2–33.8), and no female patients and 8 controls.

DISCUSSION

In this study, the long-term use of phenacetin-containing products was associated with an increased risk for renal cell cancer of about twofold for both sexes. However, the use of acetaminophen-containing products and aspirin products did not appear to elevate the risk of this cancer. For cancer of the renal pelvis, the long-term use of phenacetin- and acetaminophen-containing analgesics was associated with elevated risks of nearly threefold to eightfold. The individual effects of these analgesics could not be adequately distinguished because most long-term users took both products rather than one or the other.

Few previous studies have evaluated the role of analgesic use in renal cell cancer. A case–control study in England revealed a significant excess risk associated with daily analgesic use (*19*). Although no predominant analgesic type was reported by the daily users, 4 of the 15 patients used phenacetin products. A recent case–control study in Australia (McCredie M: Personal communication) has found a significant association with phenacetin-containing

TABLE 6.—*The OR for renal pelvis cancer associated with long-term use of acetaminophen- and phenacetin-containing analgesics*[a]

Phenacetin	Acetaminophen	Male				Female			
		Patients	Controls	OR	95% CI	Patients	Controls	OR	95% IC
None	None	23	197	1.0		9	128	1.0	
None	>36 mo	0	2	—		1	3	10.4	0.2– 768.3
>36 mo	None	1	0	—		0	5	—	
>36 mo	>36 mo	2	3	5.8	0.5–81.9	2	1	24.2	0.7–1,426.9

[a] *See* footnote *a*, table 2.

TABLE 7.—*The OR for renal pelvis cancer associated with use of aspirin products*[a]

Use	Male				Female			
	Patients	Controls	OR	95% CI	Patients	Controls	OR	95% CI
Never	7	66	1.0	—	8	54	1.0	—
Ever	43	362	1.2	0.5– 3.2	16	215	0.5	0.2– 1.4
Irregular	34	310	1.1	0.43–3.1	13	175	0.5	0.2– 1.5
Regular, ≤36 mo	2	24	1.1	0.1–11.8	1	16	0.3	0.01–4.4
Regular, >36 mo	7	28	1.5	0.3– 6.4	2	24	0.4	0.04–2.6

[a] *See* footnote *a*, table 2.

products among women but not men. On the other hand, no excess of renal cell cancer has been reported among patients with analgesic abuse or analgesic nephropathy (*1-3*). However, phenacetin has been reported to induce renal cell tumors in rats (*20*). Thus our findings suggest that renal adenocarcinomas are related to the intake of phenacetin-containing analgesics, but further study is needed before the association can be considered as causal.

Cancer of the renal pelvis has been associated with abuse of phenacetin-containing analgesics in several clinical surveys and follow-up studies of patients with analgesic nephropathy (*1*). Our study indicates that renal pelvis cancer is related to the long-term use of phenacetin-containing drugs, whereas previous studies have linked this tumor to "abuse" of these compounds. Most earlier studies were reported from areas with high rates of analgesic abuse such as Sweden, Switzerland, and Australia. On the basis of consumption patterns of the population-based controls, we found little evidence that the Minneapolis-St. Paul area has an elevated prevalence of analgesic abuse. Our findings thus suggest that the intake of phenacetin for long durations, but short of clinical abuse, could increase the risk of renal pelvis cancer.

A suggestive new finding from this study concerns acetaminophen-containing analgesics, although most patients who were long-term users also took phenacetin-containing drugs for long periods. In a case–control study of renal pelvis cancer in Australia, McCredie et al. (*4*) reported among women a significant association and a dose response for consumption of nonphenacetin analgesics, which included acetaminophen-containing drugs. Additional case–control studies by the same investigators found elevated but nonsignificant risks for men (*5*) and women (*6*) using nonphenacetin products. Moreover, clinical and experimental reports have linked acetaminophen use, both alone and in mixtures, with renal papillary necrosis, the primary lesion of analgesic nephropathy (*21*). It is noteworthy that acetaminophen (*22*) as well as phenacetin (*20*) can induce hepatocellular carcinomas in rodents (*23*). Further research is needed for an assessment of the relationship of acetaminophen, which is the major metabolite of phenacetin in the body, to cancer of the renal pelvis, inasmuch as its use is increasing, whereas that of phenacetin has been sharply decreasing due to voluntary withdrawal and governmental regulation (*23*).

The increased risk for males of renal pelvic cancer among exclusive users of aspirin is suggestive, but the absence of any excess risk among women argues against a causal relationship. Moreover, the duration of nonexclusive aspirin use among males did not suggest a dose effect. Although renal papillary necrosis can be induced in laboratory animals with aspirin alone, clinical reports of an association with aspirin alone are relatively few (*24*).

Further research is obviously needed for an assessment of the role of analgesic drugs in the development of cancers of the renal pelvis and parenchyma, as well as the lower urinary tract (*1*), and for clarification of the cancer risks and precursor lesions that may be associated with phenacetin, acetaminophen, and possibly other drugs and mixtures.

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Diet and Colon Cancer: Integration of the Descriptive, Analytic, and Metabolic Epidemiology [1]

Anthony J. McMichael *and* John D. Potter [2]

ABSTRACT—Case-control studies of diet and colon cancer have produced inconsistent findings. Data from descriptive and metabolic epidemiologic studies suggest that colon carcinogenesis varies by sex-age status, particularly when considered in relation to anatomic subsite. Thus stratification of data analysis by these criteria may elucidate dietary etiology. Consideration should also be given to the limited and nonlinear variation in colon cancer risk likely to exist in relation to the range of dietary "exposure" within Western study populations. In our community-based case-control study of colon cancer, comprising 220 patients and 440 individually matched controls, the dietary data have been analyzed by both tertile and quintile of individual consumption level. For total dietary energy intake, the tertile approach indicates a weak (men) to moderate (women) dose-response relationship; however, the quintile approach revealed in women a fourfold step-up in risk between the lowest and next-to-lowest quintile. For dietary protein, the quintile approach doubled the step-up in risk between the 2 lowest consuming categories for men compared with the tertile approach. Applying this quintile approach to data analyses stratified by sex, age, and colon subsite, we found: 1) In women, the risk of colon cancer for the upper four quintiles of consumption of calories and other major nutrients was greatest at young ages, whereas for men it was greatest at older ages. 2) The diet-associated risks tend to be maximal in the left (distal) colon for men and in the right (proximal) colon for women. Finally, total dietary energy intake was as strongly related to colon cancer risk as any specific nutrient; furthermore, the frequency of eating, after controlling for energy intake, was positively associated with risk.—Natl Cancer Inst Monogr 69: 223-228, 1985.

Despite the biologic plausibility of both dietary fiber (*1*) and fat (*2*) hypotheses in relation to colon cancer, the results of case-control studies over these past 10 years have been frustratingly inconsistent (*2-15*). As shown in table 1, a variety of nutrients or food groups have emerged as the dietary correlates of colon cancer in various individual studies.

Now this apparent inconsistency of results could actually reflect the etiologic "truth," i.e., in each different population setting, a different specific component of diet could be the primary carcinogenic "trigger" depending on the nature of the susceptibility (genetic or environmental) of the local population or on local food production and preparation practices.

Alternatively, the dietary etiology of colon cancer could be nonspecific, depending more on total food intake [and the associated mucosal cellular metabolic work (*16*)] or on frequency of eating [and the associated frequency of enterohepatic circulation of bile acids (*17*)]. If so, in each different population a different specific food may be the strongest index of these nonspecific aspects of diet.

Notwithstanding these two possibilities, a clearer pattern of findings may emerge from studies of diet and colon cancer if better account is taken of three characteristics which have an important influence, particularly when considered in combination, on the descriptive epidemiology of colon cancer: sex, age, and anatomical subsite. With few exceptions, the case-control studies listed in table 1 have not explored the relationship of sex, age, and colon subsite to diet-associated cancer risk. Often the numbers of study subjects available have been insufficient to allow such an approach.

Therefore, we considered how sex, age, and subsite may yield more, biologically plausible, information from the analysis of case-control study data. This entailed our applying various observations and ideas from our published reviews and commentaries on colon cancer (*18, 19*) to the analysis of a recently completed case-control study in Adelaide, South Australia.

We also considered how best, in a mathematical sense, to analyze data from a population setting of relative "dietary affluence," where, to put it simplistically, most of those persons who are susceptible to diet-induced colon cancer (i.e., they are at preexisting high risk for *nondietary* reasons) have indeed acquired the disease. In such a setting, which is typical of Western populations and within which most of the reported case-control studies have been done, the variation in risk in colon cancer within the range of individual dietary exposures present in the study populations may be small. Further, this variation in risk may be largely confined to one part of that exposure range. In such situations, the comparison of the high-consuming half with the low-consuming half may be inappropriate, as would the application of simple linear models.

Before applying any of these considerations to the analysis of real data, we emphasize that such approaches can be abused. They can be selectively applied to maximize the strength of relationships within one's data set. We therefore stress the importance of prior justification of such an approach to data analysis.

ABBREVIATION: RR = relative risk(s).

[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16-20, 1984.

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TABLE 1.—*Dietary factors and their relation to cancer of colon and rectum; main findings of previous case-control studies*

Factors	Relationship to risk	No. of studies	References[a]
Vegetables, cereals, fruit			
Vegetables	−	5	(*3*) (*8*) (*9*) (*11*) (*13*)
String beans	+	1	(*7*)
Fiber	−	3	(*8*) (*10*) (*12*)
Fiber	+	1	(*15*)
Rice	−	1	(*2*)
Rice	+	2	(*7*) (*13*)
Cereals	+	1	(*15*)
Fruit	−	2	(*8*)
Fruit	+	1	(*2*)
Ascorbic acid	−	2	(*8*)
Vitamin A	−	1	(*8*)
Meat, fat			
Meat	+	4	(*7*) (*8*) (*9*) (*15*)
Saturated fat/total fat	+	4	(*9*) (*12*) (*14*) (*15*)
Nonmeat protein foods			
Nonmeat protein	−	1	(*9*)
Fish	−	1	(*8*)
Milk	−	1	(*9*)
Milk	+	1	(*2*)
Dairy products, excluding milk	+	1	(*9*)
Other			
Japanese meals	−	1	(*7*)

[a] Pernu (*4*), Higginson (*5*), and Wynder and Shigematsu (*6*) found no differences between patients and controls in relation to food items.

CONCEPT JUSTIFICATION: CLUES FROM DESCRIPTIVE EPIDEMIOLOGY

Colon cancer is often said to occur at equal rates in men and women. Although perhaps true across the combined adult age range, this is *not* true within narrower age bands. In Western populations, the female incidence rate exceeds the male rate before age 50, but the situation reverses at older ages (*19, 20*). The colon cancer incidence data from South Australia for 1977–81 typify this pattern (table 2), with the male-to-female ratio increasing systematically from 0.73 at ages 25–34 to 1.27 at ages 65–74 years.

TABLE 2.—*Colon cancer: Age-specific incidence rates by sex and age ratios, South Australia, 1977–81*

Sex	Age, yr				
	25–34	35–44	45–54	55–64	65–74
Male	16.5	89.0	300.0	682.0	1,563.5
Female	22.5	101.5	295.5	597.5	1,234.0
Male-to-female ratio	0.73	0.88	1.02	1.14	1.27

This pattern is consistent with two distinct types of nonartifactual explanation. In the first explanation, exposure to exogenous carcinogens differs between the sexes in an age-dependent fashion. In the second, exposure to exogenous, early-stage carcinogens is identical in men and women, occurring usually by young adulthood, but colon carcinogenesis subsequently proceeds intrinsically more rapidly in women, reflecting differences in sex hormone status. Below, we suggest why we think the second type of explanation is more appropriate.

These sex-by-age variations in colon cancer risk are amplified further if the incidence data for colon subsites are examined. Published data suggest that the incidence of left (distal) colon cancer is more responsive to westernization of the diet (*21*), whereas the right (proximal) colon is more affected by cholecystectomy (*22, 23*). Variations in the age-specific sex ratios (male:female) of colon cancer incidence by subsite (table 3) show: 1) Below age 55, the female rate exceeds the male rate throughout the entire colon; 2) for the right colon, the female rate exceeds the male rate at all ages; and 3) from about age 55, in the transverse, descending, and sigmoid colon, male rates exceed female rates. This general pattern has also been reported in other Caucasian populations (*20*).

Clearly, either one's sex-by-age status systematically determines one's exposure to exogenous carcinogens, or *something* about sex itself influences colon carcinogenesis. The following evidence suggests it is the latter factor:

1) Six of 8 case-control studies have found the risk of colon cancer in women to be higher in nulliparous than in parous women [(*12, 24–29*); Acheson RM: Personal communication]. The investigators (*29, 30*) who examined age at first live birth both found a positive association with risk.

TABLE 3.—*Colorectal cancer incidence: Sex ratios (male-to-female) by age and subsite*

Subsite	Age, yr[a]		
	25–54	55–64	≥65
Colon			
Ascending	0.90	0.78	0.72
Transverse	0.83	1.19	1.21
Descending	0.81	2.11	1.69
Sigmoid	0.87	1.21	1.40
Rectum	0.97	1.59	2.25

[a] Calculations were based on age-standardized, sex-specific incidence rates for 2,174 patients with large bowel cancer reported to the population-based South Australian Cancer Registry during 1977–80.

2) The only 3 relevant animal experimental studies known to us have reported corroborative findings. In 1, the rate of 1,2-dimethylhydrazine-induced colon tumors was three times higher in nulliparous than in parous or breeding rats (*31*); in another, male rates clearly exceeded female rates in each of the 6 strain-by-age groups studied (*32*); in the third, butylated hydroxytoluene was shown to be protective against 1,2-dimethylhydrazine-induced tumors in male but not female rats (*33*).

3) Metabolic epidemiologic studies have shown the composition of human bile to be influenced by sex and by exogenous sex hormones, and, in women, by pregnancy and the menstrual cycle (*18*).

Hence if bile constituents, particularly the secondary bile acids produced within the gut by bacterial action, are as important in colon carcinogenesis as the available human and animal experimental evidence suggests, then the biologic plausibility of an influence of sex on colon carcinogenesis is readily apparent. With respect to a protective effect of parity, it may be relevant that the shift in estrogenic profile after completion of first pregnancy is permanent (*34, 35*). Furthermore, data from various other, often controlled, studies of human subjects indicate male-female differences in colon physiology and functioning in ways that would impart a higher risk of colon cancer to women than to men (*19*). Thus if sex-age status, particularly when considered in relation to colon subsite, influences the etiologic relationships being studied, analysis of data without reference to these 3 criteria will produce results that are quantitatively or even qualitatively misleading.

A second impediment to the informativeness of the data analysis may arise, as mentioned above, from the shape of the risk function within the exposure range existing in the study population. In a high-exposure population setting (e.g., the Western affluent diet), most of the risk variation may be confined to a small part of the exposure range in hand, e.g., within the lower end of that range, above which the risk of colon cancer plateaus. Examples of such risk functions include the confining of excess cancer risk to the lowest quintile of blood cholesterol for colon cancer in men (*36, 37*) and of blood selenium for total cancer (*38*).

Thus when one is dealing with dietary factors that influence carcinogenesis by way of a disturbance of metabolic, including hormonal, phenomena, the risk function may assume various shapes quite distinct from those characterizing the more toxicologic or directly cell-damaging effects of, e.g., nitrosamines or ionizing radiation. The shape of the risk function in figure 1, though speculative, is consistent with the sorts of examples cited above and may well approximate the relationship of various dietary factors to colon cancer. The location of a typical Western study population is shown within the exposure region of dietary affluence.

Assuming one cannot shift or widen the exposure range under study by (e.g.) the judicious inclusion of selected subcultural or ethnic groups, how does one best extract information about the diet-risk relationship? An obvious option, if study size will allow it, is for one to increase the number of exposure strata from 2 or 3 to 5. Such an approach cannot be justified if it is done in an entirely empirical and arbitrary fashion, without regard for the plausibility and meaning of the underlying risk function, or, subsequently, for the compatibility of the observed pattern with related data analyses.

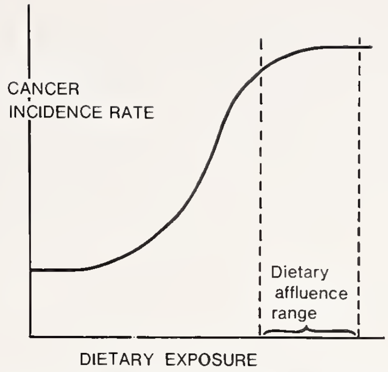

FIGURE 1.—A likely nonlinear relationship between dietary intake (exposure) and cancer incidence. The chance of one's detecting a diet-related gradient in cancer risk is strongly influenced by the range of exposure within the study population. (Within the range of dietary affluence shown, the variation in risk is both moderate and largely confined to the lower subrange of exposure.)

APPLICATION OF CONCEPTS TO ANALYTIC EPIDEMIOLOGIC DATA

A recently completed population-based case-control study of large bowel cancer in Adelaide, Australia, by one of us (JDP) has afforded an opportunity to apply these concepts. The patients were an unselected series, aged 30–74 years, as reported to the population-based Central Cancer Registry of South Australia. Controls were selected randomly from the electoral roll (voter enrollment is com-

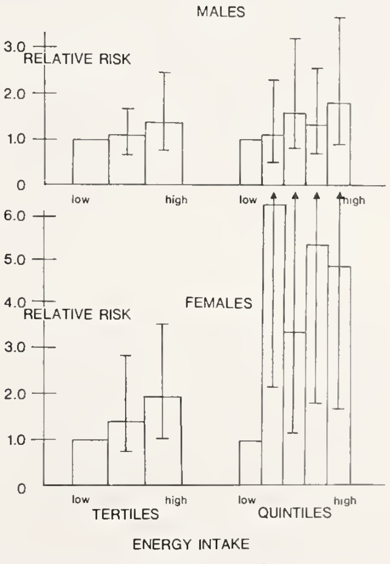

FIGURE 2.—Colon cancer and total dietary energy intake: RR and 95% confidence interval by exposure tertiles and quintiles for males and females. Lowest exposure category has RR = 1.0.

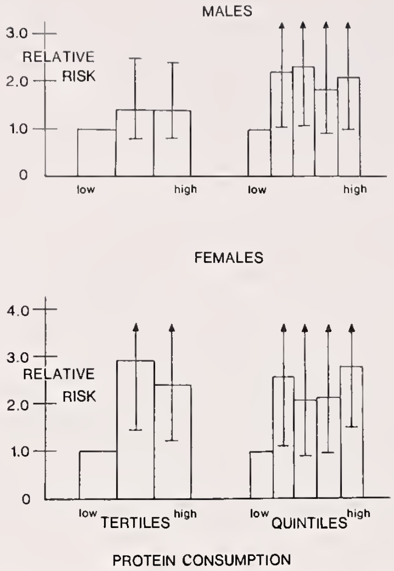

FIGURE 3.—Colon cancer and dietary protein intake: RR and 95% confidence interval by exposure tertiles and quintiles for males and females. Lowest exposure category has RR = 1.0.

pulsory) and matched on age and sex. Among the 660 participants were 99 female and 121 male patients and 440 controls. We collected dietary data by using a food frequency questionnaire as described in detail in (*39–41*). Analyses were done with the use of conditional logistic regression models (*42*).

Figures 2–4 illustrate 2 points: 1) The choice of a base line and categorization as suggested above may be important if the study population is exposed to a dietary variable at a level which does not allow a ready distinction between patients and controls but is nonetheless a likely important contributor to overall risk. 2) If indeed most of the population is exposed at a similar high level, then, above a certain point, no increase in risk is associated with increasing exposure.

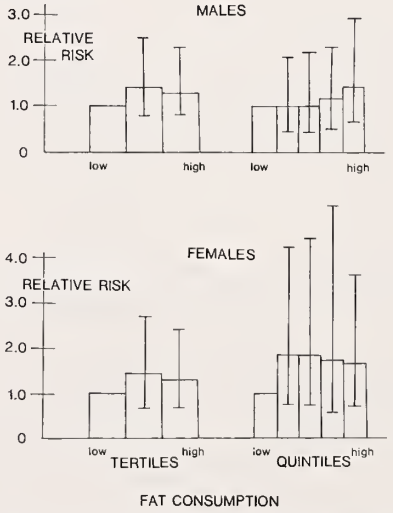

FIGURE 4.—Colon cancer and dietary fat intake: RR and 95% confidence interval by exposure tertiles and quintiles for males and females. Lowest exposure category has RR = 1.0.

TABLE 4.—*Colon cancer: Matched univariate RR (upper 80% of consumption vs. lower 20%) for specific nutrients, by age and sex*

Sex	Protein		Fat		Energy	
	<55 yr	≥55 yr	<55 yr	≥55 yr	<55 yr	≥55 yr
Male	1.5	2.2	0.2	1.3	0.2	1.7
Female	3.4	2.1	8.4	1.2	7.3	4.0

Figure 2 shows separately for men and women the RR of energy consumption by tertiles and quintiles of exposure. For males, a 40% increase in risk is associated with the highest tertile of exposure and an RR of 1.8 for the highest quintile compared with the respective base lines. For females, the differences are more pronounced, with a dose–response effect and an approximate doubling for the uppermost category when tertile analysis is considered but a general fourfold to fivefold step-up in risk for each category above the base-line quintile.

Similar analyses for protein consumption are illustrated in figure 3. Both males and females show stepwise increases in risk associated with protein consumption above the base-line category; the increase in risk for females is marginally more marked than that for males.

If real, such male–female differences could suggest that: 1) Women are more accurate at recording dietary data than men; 2) men eat relatively more food and are therefore more likely to be past the risk saturation point (*see* fig. 1); or 3) females are intrinsically more susceptible to relevant dietary exposures than males (*19*).

Figure 4 shows the same analysis for fat consumption. These data suggest that either fat is unimportant in the genesis of colon cancer, an intrinsically unlikely conclusion, given the considerable amount of epidemiologic and experimental evidence to support such a relationship, or such a high proportion of the Adelaide population is consuming above the saturation point that fat consumption level, although perhaps implicated in the promotion of bowel carcinoma, is not what distinguishes patients from controls in this particular population. That is, high fat consumption may be a necessary cause but it is not a sufficient cause; the spectrum of other influences perhaps includes age, sex, other dietary variables, genetic susceptibility, exercise, reproductive status, etc. and interactions among these.

With this base-line and categorization issue as background, we will examine the central issue of possible age–

TABLE 5.—*Colon cancer: Matched univariate RR (upper 80% of consumption vs. lower 20%) for specific nutrients, by subsite and sex*

Sex	Protein		Fat		Energy	
	Right[a] colon	Left[b] colon	Right colon	Left colon	Right colon	Left colon
Male	1.4	2.8	1.0	1.3	1.0	1.9
Female	2.3	2.9	5.0	1.4	6.7	4.1

[a] Right colon comprises cecum to hepatic flexure.

[b] Left colon comprises transverse to sigmoid colon.

TABLE 6.—*Sex-related aspects of the epidemiology of colon cancer*[a]

Descriptive epidemiology (in Caucasian populations):
- Incidence rate in women exceeds that in men at younger ages, i.e., below approximately age 55.
- For cancers of the proximal (right) colon, the rate in women exceeds that in men at all ages.

Analytic epidemiology:
- In women, colon cancer risk tends to be inversely related to parity and positively related to age at first completed pregnancy.
- After choleeystectomy, any increase in colon cancer risk tends to be greatest in women and in the proximal colon.

Metabolic epidemiology: Relative to men, women tend to have longer bowel transit times, lower fecal weights, higher fecal pH, and higher ratios of secondary to primary bile acids.

[a] *See* text for reference citations.

TABLE 8.—*Female colon cancer: Conditional multiple logistic regression of cancer risk on frequency of eating and dietary energy intake*[a]

Diet variable	RR	95% Confidence interval
Daily frequency of eating		
≤3	1.0	
4	.8	0.4–1.6
≥5	1.7	0.9–3.1
Energy intake quintiles		
1	1.0	
2	6.1	2.0–18.2
3	3.6	1.2–10.7
4	5.3	1.8–15.7
5	4.6	1.6–13.6

[a] Likelihood ratio test statistic is $\chi^2_6=21.35$; $P=.002$.

sex-subsite differences in relation to diet and colon cancer.

The RR associated with the upper 4 quintiles [compared with the lowest quintile (RR = 1.0)] as a single estimate are given in tables 4 and 5. As figures 2–4 show, the saturation of risk makes this a meaningful summary estimate, though clearly it is inappropriate for one to draw any statistical significance from such figures; we use them only to demonstrate a pattern of differences more clearly.

Whereas RR increases with age for higher nutrient exposure for males, it decreases for females, as illustrated in table 4, in which the relationships among nutrients consumed are given by age and sex. These findings are consistent with the descriptive and metabolic epidemiologic data regarding male–female differences in risk of colon cancer. As noted in table 2, women have higher rates of colon cancer than men at younger ages, with the crossover in risk occurring at age 55. The metabolic epidemiology shows that women compared with men on similar diets have higher gut pH, more secondary bile acids within their bile, lower fecal weights, and longer transit times; all these factors are liable to increase risk in women compared with men (*19*).

TABLE 7.—*Male colon cancer: Conditional multiple logistic regression model of cancer risk on frequency of eating and dietary energy intake*[a]

Diet variable	RR	95% Confidence interval
Meal frequency		
≤3	1.0	
4	1.3	0.7–2.4
≥5	1.6	0.9–2.7
Energy intake quintiles		
1	1.0	
2	1.1	0.5–2.3
3	1.7	0.8–3.3
4	1.3	0.6–2.5
5	1.5	0.7–3.2

[a] Likelihood ratio test statistic is $\chi^2_6=5.99$; $P=.43$.

In similar fashion, the male–female differences in risk at colon subsites for exposure to higher levels of nutrient consumption are presented in table 5. In males, colon cancer in the distal section is associated with higher RR than that of the proximal colon. In females, apart from protein exposure, the pattern is the reverse. These findings too are consistent with the descriptive epidemiology of male–female differences (tables 3, 6) that suggests cancer in the proximal section of the colon is commoner in females at all ages and that cancer in the distal section is commoner in males at older ages.

As noted in figure 2, total dietary energy intake, a less specific characteristic of diet, is also related to colon cancer risk particularly in women. Conditional logistic regression models are shown separately for males and females in tables 7 and 8. Meal frequency in women may be a risk factor for colon cancer, independent of total dietary intake. The pattern in males is consistent but not statistically significant. This finding may suggest that total energy intake (more related to mucosal cellular work load and cell turnover) and frequency of eating [a marker for bile recirculation frequency and therefore the ratio of secondary to primary bile acids (*43*)] are both important in colon carcinogenesis.

CONCLUSION

In conclusion, we would like to return to our original theme. The inconsistencies that have been observed in dietary studies may be related to the degree of risk saturation for a given nutrient in any one population, and, furthermore, may partly reflect a failure by investigators to stratify by age, sex, and subsite.

Some considered exploration of data for evidence of these effects appears to be a proper pursuit for epidemiologists concerned to integrate descriptive, analytic, and metabolic epidemiology. The related findings for these areas are summarized in table 6.

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Case–Control Study of Urinary Bladder Cancer in Metropolitan Nagoya [1, 2]

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ABSTRACT—We conducted a population-based case-control study of patients with bladder cancer and of controls drawn randomly from the general population of Metropolitan Nagoya and interviewed both groups. The incidence rates of bladder cancer were 2.42 and 7.05/100,000 for females and males, respectively. The analysis, based on 293 patients and 589 controls who were frequency matched for age, sex, and residence, provided the following major findings. Age-adjusted relative risks of 1.89 (1.15–3.10) and 3.53 (1.71–7.27) were found in male and female cigarette smokers, respectively. Significant relative risk was also found in males who drank cocoa. Elevated risk with a dose-response relationship was observed among women who used hair dye and who smoke, but this risk was insignificant, with the disappearance of a dose-response relationship, when it was adjusted for smoking. Age- and smoking-adjusted relative risk of coffee drinking was insignificant with no dose-response relationship. Relative risk of artificial sweetener use was below 1 with adjustment for age and smoking. Intake of alcoholic beverages and cola was insignificantly associated. Reduced risk of significance was suggested for the intake of black tea and matcha (powdered green tea) in females and of fruit juice in males.—Natl Cancer Inst Monogr 69: 229–234, 1985.

Bladder cancer occurs worldwide, but it is a relatively infrequent type of cancer in most countries (*1*). Risk factors in the development of human bladder cancer are thought to be use of tobacco, occupational exposures to certain chemical carcinogens, infection with *Schistosoma haematobium*, and possibly coffee drinking, use of artificial sweeteners, analgesics abuse, and urine stasis (*2*). Ingestion of bracken fern is considered potentially hazardous (*3*). Some endogenously produced metabolites of the tryptophan–nicotinic acid pathway are also presumed to be responsible for some human bladder cancers in patients with no apparent industrial exposure to chemical carcinogens (*4*). An investigation of dietary factors indicates the association of bladder cancer with low levels of vitamin A intake and with infrequent consumption of carrots, milk, and cruciferous vegetables (*5*).

With these suggested risk factors in mind, we undertook an international case–control study of urinary bladder cancer in Boston, Massachusetts; Nagoya, Japan; and Manchester, England (*6–10*). Here we deal mainly with the findings from the analysis of the Nagoya data. Some of the results that are given have appeared in slightly different form elsewhere (*6, 7, 10*).

MATERIALS AND METHODS

We conducted this study from January 1976 to December 1978, in Metropolitan Nagoya, which includes the city of Nagoya and 10 surrounding cities and towns.

Case identification.—We identified cases of urinary bladder cancer through the Nagoya Bladder Tumor Registry, which has been in operation since 1974; the Registry obtains data from 19 hospitals and responsible urologists in the Nagoya area. Completeness of registration is nearly 100% (Obata K: Unpublished observations).

To be eligible for the present study, a patient must have received an initial diagnosis of a primary neoplasm of the lower urinary tract, i.e., bladder, ureter, renal pelvis, and urethra. In addition, patients had to be 20 years of age or older and residents of Metropolitan Nagoya at the time of diagnosis. Patients aged 90 years or over were ineligible for interview. Tumors throughout the histologic spectrum from papilloma to invasive neoplasia were included.

Control selection.—We selected controls by random-sampling procedures from the general population, using the electoral registers for the study period from 1976 to 1978. Electoral registers are updated annually and are a nearly complete list of residents aged 20 years or older. The sampling was designed to select twice as many controls as patients by frequency matching procedures. The age and sex distribution of patients was determined by the distribution in the previous 2 years of 1974 and 1975. Controls were also matched for residence in Nagoya City versus one of the surrounding communities.

Data collection.—Epidemiologic information was collected by direct interviews conducted by 3 public health nurses who had many years of experience doing similar interviews. They attempted to interview each eligible subject, but if a subject was too ill, had died, or could not be contacted, they tried to interview a proxy, i.e., a relative familiar with the subject's background and habits. The initial contact with a subject was by letter and was followed by a telephone call by 1 of the clerks to schedule an interview. The actual interviews were usually conducted at the subjects' homes, but some were interviewed during an

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ABBREVIATION: RR=relative risk(s).

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TABLE 1.—*Smoking habits and urinary bladder cancer risk of residents in Metropolitan Nagoya*

Sex	Age, yr	Subjects	Smokers	Nonsmokers	RR	95% Confidence interval
Male	20–44	Patients	15	5	.82	0.21–3.22
		Controls	22	6		
	45–64	Patients	81	6	1.70	0.65–4.42
		Controls	143	18		
	65–89	Patients	108	12	2.37	1.23–4.57
		Controls	201	53		
	Total	Patients	204	23	1.87	1.14–3.05
		Controls	366	77		
					1.89	1.15–3.10[a]
Female	20–64	Patients	12	17	4.50	1.63–12.39
		Controls	8	51		
	65–89	Patients	8	29	2.72	0.96–7.74
		Controls	8	79		
	Total	Patients	20	46	3.53	1.73–7.21
		Controls	16	130		
					3.53	1.71–7.27[a]

[a] This is the age-adjusted RR (maximum likelihood estimate).

outpatient visit or hospital stay. When responses were vague or answers were missing in the editing of each questionnaire, an interviewer attempted to obtain the information by telephone.

Epidemiologic items surveyed by interview included: routine demographic data, such as date of birth, educational attainment, and religion; consumption of various beverages, such as coffee, black tea, soft drinks, and alcoholic beverages; smoking habits; use of sugar substitute or artificial sweeteners; occupational histories; use of hair dyes; habitual intake of drugs containing phenacetin and phenazone; and previous episodes of illness. Information collected on each cancer patient included name of hospital and attending urologist, dates of admission and discharge, discharge diagnosis, treatment regimens, and pathologic diagnosis. All the epidemiologic information collected was processed on a FACOM M-200 computer at Nagoya University Computation Center.

RESULTS

During the study period of 3 years, we identified 345 eligible patients (20–89 yr old) and selected at random 735 controls. Among the 345 identified, 293 (84.9%) were successfully interviewed. Among the 735 randomly selected controls, an interview was completed with 589 (80.1%).

Because the present study is a population based case–control study, the incidence figure of urinary bladder cancer could be obtained. The number of incident cases collected in 3 years was 259 in males and 86 in females. These figures yielded an annual crude incidence rate of 2.42 and 7.05/100,000 for females and males, respectively.

We obtained specimens for slides from 287 (83.2%) of the 293 patients interviewed. About 28% of these slides were of materials from cystectomies and the remaining were from biopsies. Among these, 241 slides were of sufficiently good quality for us to perform detailed evaluations. The primary histologic type (99.6%) was transitional cell carcinoma. Undifferentiated carcinoma accounted for only 0.4%. Squamous cell carcinoma and adenocarcinoma were not identified as primary histologic types, but a secondary squamous cell component was observed in 2% of the patients (*8*).

Table 1 shows the RR for bladder cancer incidence of smokers compared with nonsmokers. Male smokers demonstrated a 2.37 RR in the 65- to 89-year-old age group and a 1.87 RR in all ages. When age was adjusted by the maximum likelihood method, the RR of smokers was found to be 1.89, significantly larger than unity. In females, age-adjusted RR of smokers was 3.53, much higher than in males.

The relationship of coffee drinking to bladder cancer

TABLE 2.—*Relationship of coffee drinking and urinary bladder cancer risk in residents in Metropolitan Nagoya*[a]

No. of cups of coffee consumed/day	Males				Females			
	Patients	Controls	RR	95% Confidence interval	Patients	Controls	RR	95% Confidence interval
None	72	137	1.00		39	77	1.00	
<1	44	112	.73	0.46–1.15	13	41	.65	0.30–1.39
1	43	92	.64	0.40–1.04	11	18	.82	0.32–2.13
2–3	54	86	1.15	0.73–1.82	2	9	.56	0.11–2.91
4+	12	12	1.76	0.74–4.19				

[a] The RR are adjusted for age and smoking (nonsmoker, smoker), i.e., adjusted for the maximum likelihood estimate.

TABLE 3.—*Relationship of use of hair dye and urinary bladder cancer risk in females in Metropolitan Nagoya*[a]

Use of hair dyes by:	Not tinted	Frequency	
		<1/mo	≥1/mo
Nonsmokers			
Patients	21	12	12
Controls	56	38	33
Crude RR	1.00	.84 (0.37–1.92)	.97 (0.42–2.23)
Smokers			
Patients	2	8	10
Controls	10	4	2
Crude RR	1.00	10.00 (1.56–63.97)	25.00 (3.48–179.86)
Maximum likelihood estimates	1.00	1.31 (0.64–2.71)	1.70 (0.82–3.52)

[a] *Numbers in parentheses* are 95% confidence limits.

incidence is given in table 2. The degree of coffee consumption was measured by cups of coffee drunk per day. The RR adjusted for age were obtained by the maximum likelihood method; none reached the significance level, which indicates that the usual consumption of coffee seems to hold little risk for bladder cancer in Japan.

Few males use hair dye, so no statistical evaluation could be made. In table 3, RR adjusted for smoking as well as age are presented. Among female nonsmokers, users of hair dye showed insignificant RR compared with nonusers. In contrast, among female smokers, RR with dose–response relationships of 10.00 and 25.00 were demonstrated among those who dyed their hair, though the numbers in each cell of the table are inadequately small. When adjusted for smoking, the RR for 2 categories of hair dye use fell to an insignificant level.

In our study of the relationship between the use of artificial sweeteners and bladder cancer incidence, we calculated the RR by contrasting subjects who used such sweeteners with those who did not (table 4).

In males, the RR without adjustment was 0.68. When age and smoking were adjusted or in combination, RR were virtually unaltered. In females, crude and adjusted RR of users were 0.43 or 0.45, slightly smaller than in males.

Table 5 summarizes the crude and adjusted RR of the ingestion of various beverages for bladder cancer incidence, contrasting subjects who "ever used" with the "not used."

In males, we found significant RR of 2.88, 2.82, and 2.77 in those who drank cocoa with and without adjustment for age or smoking. Seemingly, the smallest RR were found among fruit juice drinkers. In females, no significantly large RR were noted with the ingestion of any beverage. Ever drinkers of black tea and matcha (powdered green tea) were at lesser risk of bladder cancer when adjusted for age as well as when not adjusted, but not when adjusted for smoking. Female fruit juice drinkers were not at less risk for bladder cancer.

DISCUSSION

The present study is a population-based case–control study in which incident cases are histologically confirmed and controls are drawn randomly from the general population. To our knowledge, this is the first study in Japan in which electoral registers were used as a source of controls. Because of the methodologic features outlined above, an annual incidence rate of urinary bladder cancer could be readily obtained: 2.42 and 7.05/100,000 in females and males, respectively. These figures are higher, by about 34% in males and about 57% in females, compared with the incidence rates obtained from the Miyagi Cancer Registry (*11*). These higher figures may be due to our deliberate effort to include all incident cases, even papillomas.

Smoking is consistently incriminated as a risk factor in the development of human bladder cancer. A number of investigators (*12–19*) have indicated the positive relationship, as well as those who conducted follow-up studies of smokers and nonsmokers (*20–22*). In general, smokers have a two to three times greater risk of bladder cancer than do nonsmokers (*23*). Cigarette smokers in our present study demonstrated age-adjusted RR of 1.89 in males and 3.53 in females.

Among Caucasians, the RR of female smokers for bladder cancer is equal to or less than that for males who smoke (*23*). The much larger RR found in females in Japan may be ascribed to chance, but the following situation may be relevant to this finding. In Japan, the average percentage of smokers was only 15.6 among females aged 20 years or older during 1976–78 (*24*). Smoking was more prevalent among working women, e.g., 42.1% of service workers and saleswomen; 23.9% of the proprietresses and those in merchandising; 20.8% of executives and professionals; and 13.2% of the housewives (*24*). Thus women

TABLE 4.—*Relationship of use of artificial sweeteners and urinary bladder cancer risk in residents in Metropolitan Nagoya*[a]

Users	Used		Crude RR	RR (maximum likelihood estimates) adjusted for:		
	Ever	Not		Age	Smoking	Age and smoking
Males						
Patients	102	122	.68	.67	.68	.67
Controls	238	194	(0.49–0.94)	(0.49–0.93)	(0.49–0.94)	(0.49–0.93)
Females						
Patients	25	40	.45	.43	.45	.45
Controls	83	60	(0.25–0.82)	(0.23–0.79)	(0.24–0.84)	(0.24–0.84)

[a] *See* footnote *a*, table 3.

TABLE 5.—*Relationship of drinking beverages and urinary bladder cancer risk in residents in Metropolitan Nagoya*[a]

Beverage	Subjects	Used		Crude RR	RR (maximum likelihood estimates) adjusted for:		
		Ever	Not		Age	Smoking	Age and smoking
	Males						
Black tea	Patients	88	139	.90	.90	.96	.95
	Controls	183	260	(0.65–1.25)	(0.65–1.25)	(0.69–1.33)	(0.68–1.32)
Matcha	Patients	55	170	1.02	1.05	1.08	1.05
	Controls	105	331	(0.70–1.48)	(0.72–1.54)	(0.74–1.57)	(0.73–1.51)
Cola	Patients	62	165	1.04	1.00	1.04	1.00
	Controls	118	325	(0.72–1.48)	(0.69–1.44)	(0.72–1.49)	(0.69–1.44)
Cocoa	Patients	11	216	2.77	2.88	2.82	Not calculable
	Controls	8	435	(1.14–6.75)	(1.18–7.04)	(1.15–6.91)	
Fruit juice	Patients	83	144	.73	.72	.73	.72
	Controls	196	247	(0.52–1.01)	(0.52–1.01)	(0.53–1.02)	(0.52–1.00)
Alcoholic beverages	Patients	157	70	.88	.84	.83	.81
	Controls	144	299	(0.62–1.25)	(0.60–1.22)	(0.58–1.19)	(0.56–1.15)
	Females						
Black tea	Patients	24	41	.50	.49	.57	.55
	Controls	79	67	(0.27–0.90)	(0.27–0.89)	(0.31–1.05)	(0.29–1.03)
Matcha	Patients	11	55	.45	.44	.50	Not calculable
	Controls	44	98	(0.22–0.92)	(0.21–0.92)	(0.24–1.05)	
Cola	Patients	10	56	.66	.64	.65	" "
	Controls	31	115	(0.30–1.44)	(0.29–1.41)	(0.29–1.44)	
Cocoa	Patients	0	66	Not calculable	Not calculable	Not calculable	" "
	Controls	4	142				
Fruit juice	Patients	33	33	1.09	1.08	.99	.99
	Controls	70	76	(0.61–1.95)	(0.60–1.93)	(0.54–1.81)	(0.54–1.82)
Alcoholic beverages	Patients	19	47	.63	.61	.57	.55
	Controls	57	89	(0.34–1.18)	(0.32–1.15)	(0.30–1.10)	(0.28–1.07)

[a] *See* footnote *a*, table 3.

who smoke seem to belong to a particular socioeconomic and cultural segment and thus may be more likely to be influenced by hazardous environments or inadequate hygienic or dietary practices.

A significant association between coffee consumption and bladder cancer was originally reported in 1971 by Cole (*25*). A number of subsequent studies have appeared with inconsistent patterns of association by sex and race (*5, 14, 26-28*). Associations, even when found, are generally weak and sometimes absent (*19, 29*) or negative (*27*). In the present study, neither an association between coffee drinking and bladder cancer incidence nor a dose–response relationship was found, when analyzed with or without adjustment for age and smoking.

Use of hair dye was also incriminated as a possible risk factor for human bladder cancer. This association has been measured mostly by observation of the risk for barbers, hairdressers, beauticians, or cosmetologists, or the risk for those who dye their hair (*30*). No suggestive association with bladder cancer emerged from the previous investigations (*31-35*).

In our investigation, female smokers demonstrated an increased risk with a clear dose–response relationship, but female nonsmokers did not. When smoking was adjusted, however, significance of the RR as well as the dose–response relationship disappeared. This indicated that hair dye use was strongly linked with smoking habits, and no serious direct effects of ordinary coloring on bladder cancer development seems likely.

The first large-scale study in Canada (*36*) demonstrated a positive association between consumption of saccharin and bladder cancer development in men, but not in women. However, in a case–control study conducted in several metropolitan areas in the United States, Hoover and Strasser (*37*) reported no evidence of a strong or moderate carcinogenic effect of artificial sweetener use on the human bladder, but they concluded that artificial sweetener use in the past may have had a minimal effect on bladder cancer rates. We determined no increase in risk for bladder cancer among users of artificial sweeteners; this finding is in line with other investigations (*9, 14, 16, 19, 38-41*). However, we found RR significantly less than 1 in both sexes. The explanation for this peculiar finding is not known; it is not explained by such factors as interview quality, biases in selecting cases and controls, and potential confounding variables. Morgan and Jain (*19*) also observed a significantly low RR (.35) for females who consumed artificial sweeteners compared with controls, but not for males. Their explanation was that patients with bladder cancer might be demonstrating a lower use of artificial sweeteners because of unascertained differences in both patients and controls who may have other diseases, e.g., hypertension, obesity, or diabetes.

A few reports were concerned with beverages other than coffee as possible risk factors for bladder cancer. Morgan and Jain (*19*) concluded that alcohol and cola intake increased the RR of bladder cancer among male smokers, which suggests that smoking interacts with alcohol and cola intake in the production of bladder cancer. In contrast, both alcohol and cola consumption were insignificantly related to bladder cancer in a recent study (*16*). Neither alcohol nor cola intake demonstrated a significant association with bladder cancer risk, when we did our analysis with or without adjustment for age and smoking. However, black tea and matcha may be associated with the reduced risk of bladder cancer in females, but not in males. Tea intake was insignificantly associated in the study by Morgan and Jain (*19*).

We did detect that cocoa intake was a significant risk factor for males, even when adjusted for age and smoking, but not for females. Apparently this association has not been reported elsewhere, though it may pertain to some multiple comparison problems. Fruit juice intake, in contrast, was suggested to be associated with the reduced bladder cancer risk only in males.

Beverages, such as black tea, matcha, cocoa, and fruit juice were associated with bladder cancer risk inconsistently by sex, and, therefore, a strong emphasis should not be placed on these findings. However, intake of matcha and fruit juices, which are rich in ascorbic acid, is suggested to protect against the development of bladder cancer.

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Religion and Cancer in Los Angeles County [1, 2]

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ABSTRACT—The patterns of cancer risk by religion in the large multidenominational population of Los Angeles County were examined with the method of proportional incidence. Risk estimates for individual cancers by religion were screened and those extreme but stable estimates found were reexamined in light of relative socioeconomic class, nativity, and ethnicity. Within Protestant denominations, gradients which can still best be attributed to religious preference were observed for leukemia, stomach, and cervix cancer. Roman Catholics tend to have high risks of stomach and gallbladder and a low risk of prostate cancer, whereas Eastern Orthodox women trade high risk of stomach cancer for low risk of endometrial and lung cancer. The most extreme pattern of risk, that for Jews, is comprised of lowered risk for cervical cancer and for most sites usually associated with smoking, plus consistently higher risk for lymphomas, thyroid cancer, and bladder cancer among males. Like Jews, Seventh-Day Adventists experience high risk for lymphoma and low risk for cervical and respiratory cancers. Risk to Mormons in Los Angeles differs from that of the standard Protestant population in only minor and inconsistent ways. Neither Mormons nor Adventists showed the previously reported deficits of colorectal or breast cancer. Although the method of proportional incidence may be partly responsible for our failure to confirm previous findings, nonreligious cultural or methodologic factors in the original investigations also provide plausible explanations. More generally, associations of the modest magnitude observed between cancer risk and religion in American populations should probably not be attributed to religious life-style, unless extraordinary circumstances permit the exclusion of other determinants.—Natl Cancer Inst Monogr 69: 235-245, 1985.

Differences in risk according to religious affiliation have often been used in connection with knowledge of religious life-style for the generation of hypotheses of etiology for cancer and other diseases. Most sources of information only permit a comparison between the members of one religion and all other members of the same community or cohort, and most do not permit a clear distinction to be made between religious affiliation and social class, nativity, and ethnic origin, much less between religion and other specific aspects of life-style.

The population of Los Angeles County is extremely diverse with respect to religion as well as social class, nativity, and ethnicity. In this paper, we describe the patterns of cancer occurrence according to stated religious affiliation; evaluate the degree to which these patterns reflect social class, nativity, and ethnicity; and compare our findings with those of previous observers.

MATERIALS AND METHODS

The University of Southern California Cancer Surveillance Program identifies each Los Angeles County resident in whom cancer is microscopically verified or for whom cancer is recorded on a death certificate (*1*). Using the hospital pathology report and medical record, we classified tumors by anatomic site and histologic morphology. Each case identified by the Registry is routinely characterized by date of birth, sex, race, birthplace, religion, and residential address. We use the residential address to characterize each case by a socioeconomic classification, which is based on the aggregation of 1970 census tracts in the County into rough quintiles using the median income of the families and the mean years of education of heads of households in each tract. Surnames are classified according to an augmented version of the 1970 census list of Spanish surnames (*2*); the non-Spanish surnames are then subdivided into ethnic categories on the basis of name etymology, U.S. genealogy, and recorded evidences of Los Angeles ethnic affiliation, such as ethnic telephone directories.

Of the 266,024 records abstracted during the period 1972–81, 20% provide for no specification of the patient's religion. About 4% of all cancer patients either choose not to indicate a religious affiliation or designate themselves as "atheist" or "agnostic." The remaining patients are subdivided into approximately 100 religious categories; however, among these are Christian and Protestant without further specification, into which approximately 30% of men and women place themselves. We excluded each of these noninformative individuals, as well as the nonwhite and Spanish-surnamed patients, and those belonging to non-Christian religions (Buddhism, Islam, Hinduism, Theosophy, Vedanta, Baha'i, Shinto, Spiritualism, and others), which in Los Angeles are each represented by a few white patients. The remaining 94,886 white, non-Spanish surnamed patients diagnosed from 1972 to 1981, with specific religious designations, were available for study. These could be subdivided into Jews, Mormons, Seventh-Day Adventists, Christian Scientists, Jehovah's Witnesses, Roman Catholics, Eastern Orthodox, and Protestants. The latter were further subdivided into Unitarians, Quakers, Congregationalists, Presbyterians, Methodists,

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ABBREVIATION: PIR = proportional incidence ratio(s).

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Lutherans, Baptists, and other (mostly fundamentalist) Protestant denominations (*3, 4*).

The above list of denominations was submitted independently to 4 experts on religious life-style in Los Angeles (1 sociologist and 3 theologians from different denominations), who were also provided with a list of 5 criteria designed to measure degree of fundamentalism: presence of church rules regarding sexual practice, theological dogmatism, prevalence of Christian family life, clean life-style, and church-oriented life-style. None of these criteria was further defined, and the experts were asked to rank each religion on a scale of lesser to greater fundamentalism (no weighting scheme for the various criteria was specified). The Protestant subcategories were listed by the experts with general agreement in the order in which they are listed above, and these were then arbitrarily combined into 3 subcategories. Protestant A (least fundamentalist and least evangelical), comprised of the first 4 denominations listed above; Protestant B (not strongly evangelical but with a spectrum of fundamentalism), comprised of Methodists and Lutherans; and Protestant C (most fundamentalist and most evangelical), comprised of Baptists and the other smaller Protestant denominations. Although the Protestant A and B patients proved to be roughly evenly divided among the various denominations subsumed, the Protestant C category consisted mostly of Baptist patients. Jews as a group were placed by the experts in a scale position between the Protestant A and B groups; Christian Scientists, Eastern Orthodox Christians, and Roman Catholics were placed on the scale in that order between the B and the C groups; and Jehovah's Witnesses, Seventh-Day Adventists, and Mormons were listed in that order of increasing fundamentalism after Protestant C. Because of the inevitable misclassifications and misinterpretations which would result if reliance were placed on this arbitrary scale in its entirety, we made no use of it other than to retain the ordered tripartite subcategorization of Protestants.

Because the census information does not enumerate residents by religious affiliation, no direct incidence computations are possible. Therefore, we compared cancer patterns between religions by using and comparing PIR for cancers at each of 19 anatomic sites (table 1). This was done for each age-sex category by division of the observed number of cases of a specified neoplasm in the members of a denomination by an expected number obtained as follows: Within each age-sex group, the total number of cancer cases in that denomination is multiplied by the proportion of cases of that cancer among all (arbitrarily) Protestant B white cancer patients of that age and sex, and these age-specific numbers are then summed. The resulting indirectly age-adjusted ratios can be compared directly, provided that no more than one of the following two conditions apply: extreme variations in the age distribution of patients in the several denominations, and strong variation in the risk attributable to the various denominations by age. Among the 10 religious categories, the percent of patients 65 or over varied from about 40% (Jehovah's Witnesses, Seventh-Day Adventists) to about 60% (Eastern Orthodox, Christian Scientists).

We used a likelihood ratio test (chi-square with 1 degree of freedom) to compute confidence limits around the PIR calculated for each religious subgroup referent to members of the Protestant B denomination.

We screened the risk estimates to select neoplasm-religion combinations for further consideration. The 3 criteria which had to be satisfied were: extreme PIR (<0.8 or >1.2), improbability of chance as an explanation (95% confidence limits exclude 1.0), and level of importance (expected or observed cases >10). For each combination worthy of further consideration on these grounds, another estimate of the PIR was computed by the same method, except that within each age category the expected numbers were computed separately for each of the 3 major social classes before summing, thereby providing an estimate of risk less confounded by social class.

Those estimates that remained extreme and significant after this adjustment were next examined for possible confounding by nativity. Mormons were dichotomized into those born in the Mountain States and those born elsewhere; Protestant C patients into those born in the Southern states (South Atlantic, East South Central, and West South Central) and those born elsewhere; and Jews, Roman Catholics, and Eastern Orthodox patients were divided into immigrants and U.S. natives. None of the other religious denominations subsume sizable pertinent nativity subgroups. If an extreme risk (<0.8, >1.2) for the particular pertinent nativity in 1 of these 5 religious groups was found, the PIR for that neoplasm was recomputed within the nonspecific (i.e., the other or local) nativity stratum.

Although we performed no other formal stratified analyses, the final step was a comparison of the distribution of ethnicity (as evidenced by surname) between Protestant B patients and those of each of the other denominations to evaluate the plausibility of inherent confounding on the basis of ethnic origin. For each interesting neoplasm-religion combination, these adjustments and comparisons are summarized.

Because our findings with respect to Mormon and Adventist residents of Los Angeles differ from earlier findings, both morbidity information from Utah (*5*) and mortality information from the American Cancer Society-Seventh-Day Adventist volunteer cohort (*6*) were analyzed in conjunction with the Los Angeles study and comparison groups; the PIR were calculated for the original religious subgroups in comparison with the Los Angeles standard as well as for the Los Angeles religious groups in comparison with the original standards. Because of limitations in available detail, the analysis was confined to persons 35 years of age or older.[4] Mortality estimates for religious subgroups in Los Angeles were computed under the assumption that sex- and age-specific mortality-to-incidence ratios by cancer site for non-Spanish surnamed whites in Los Angeles do not vary by religion.

RESULTS

In table 1 are shown PIR for each site-sex-religion combination, with the number of observed cases and an

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[4] Age-specific data for Utah was made available by Dr. Joseph L. Lyon.

TABLE 1.—*The PIR by sex and religion, Los Angeles County, 1972–81*[a]

Neoplasm	Sex	Religion																			
		Jewish		Seventh-Day Adventist		Mormon		Christian Scientist		Protestant						Jehovah's Witnesses		Roman Catholic		Eastern Orthodox	
										A		B[b]		C							
		PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients	PIR	No. of patients
Melanoma	M	1.2	324	1.2	5	1.5[c]	52	1.1	8	1.4[c]	107	1.0	130	0.8[c]	59	1.0	7	0.8	450	0.6	11
	F	1.1	330	1.0	8	0.9	32	1.0	18	1.0	107	1.0	150	0.8	71	0.9	8	0.8[c]	442	0.3[c]	4
Leukemia	M	1.2[c]	307	1.5	7	1.4	41	1.8	12	1.8	82	1.0	111	1.1	77	1.5	7	1.0	443	1.2	12
	F	1.0	220	0.6	4	1.1	28	1.0	19	0.7[c]	58	1.0	112	1.2	76	1.6	9	1.0	389	0.6	6
Lymphoma	M	1.4[c]	610	1.7[c]	13	1.1	53	1.0	12	1.0	127	1.0	195	0.9	103	1.2	11	1.0	765	1.0	26
	F	1.5[c]	630	1.7[c]	20	1.2	52	1.1	33	1.0	140	1.0	200	1.2	136	0.9	11	1.2	801	1.2	21
Thyroid	M	2.3[c]	145	1.4	2	0.7	6	1.1	2	1.0	18	1.0	30	0.9	16	0.5	1	0.8	107	1.7	7
	F	1.8[c]	312	1.1	5	1.1	25	0.5	4	0.7	43	1.0	84	1.1	60	1.6	9	1.0	351	1.2	9
Colon	M	1.3[c]	1,302	0.9	15	1.0	90	1.1	36	0.9	251	1.0	462	0.8[c]	184	1.3	22	1.2	1,678	0.9	58
	F	1.0	1,275	0.9	33	1.0	112	1.0	107	1.0	486	1.0	629	1.0	357	1.0	30	1.1	2,020	0.8	48
Rectum	M	0.8	279	0.8	4	0.7	23	1.5	17	0.8	80	1.0	160	1.0	83	1.4	8	1.1	656	0.8	17
	F	0.8[c]	226	1.3	12	0.6[c]	15	1.1	28	0.9	101	1.0	153	1.0	80	1.0	7	1.2	541	1.5	20
Pancreas	M	1.3[c]	329	1.0	4	1.0	24	1.0	8	1.0	68	1.0	115	0.9	51	0.7	3	1.0	421	0.8	13
	F	1.4[c]	336	1.0	7	0.9	19	0.6	3	0.9	85	1.0	123	1.0	66	1.1	6	1.1	400	1.2	13
Bladder	M	1.4[c]	965	1.1	13	1.0	68	1.1	26	1.2	261	1.0	341	0.9	159	1.1	13	1.1	1,306	1.2	59
	F	1.0	329	0.6	6	1.1	31	1.1	30	1.0	125	1.0	167	0.9	79	0.7	5	1.0	517	1.0	15
Lung	M	0.7[c]	1,160	0.7[c]	18	0.9	144	0.8[c]	42	0.9	450	1.0	804	1.2	505	1.0	26	1.1	3,382	1.0	98
	F	0.9	877	0.4[c]	12	1.0	94	0.8[c]	52	0.9	318	1.0	498	0.9	248	1.1	23	1.1	1,827	0.7[c]	31
Larynx	M	0.7[c]	164	0.6	2	0.5[c]	11	0.6	4	1.0	66	1.0	108	1.0	58	1.4	5	1.1	440	1.3	18
	F	0.6	37	—	0	1.2	6	0.3	1	1.6	30	1.0	26	1.1	16	—	0	1.2	107	0.9	2
Oral	M	0.4[c]	177	0.8	5	1.1	48	0.5[c]	7	1.0	121	1.0	206	1.1	121	0.5	4	1.0	791	0.8	21
	F	0.6[c]	144	0.5	3	1.2	6	0.7	11	1.2	101	1.0	117	1.4[c]	91	0.8	5	1.2	460	1.0	10
Esophagus	M	0.6[c]	44	—	0	1.3	9	0.9	2	1.1	24	1.0	35	1.5	27	1.6	2	1.4[c]	177	0.9	4
	F	1.1	55	—	0	1.7	8	1.6	6	1.2	23	1.0	25	0.7	9	—	0	1.5[c]	112	1.3	3
Stomach	M	1.3[c]	400	0.2[c]	1	0.7	21	1.2	12	0.7[c]	60	1.0	146	0.9	70	2.0[c]	11	1.1	593	1.4	27
	F	1.4[c]	301	0.8	5	1.1	21	1.0	19	1.0	79	1.0	107	1.4[c]	78	1.4	7	1.4[c]	451	2.8[c]	27
Gallbladder	F	0.9	51	1.7	3	1.0	5	0.6	3	0.8	17	1.0	29	0.5	8	3.7[c]	5	1.5[c]	128	2.2	6
Cervix	F	0.3[c]	106	0.6	5	1.0	38	1.5[c]	27	0.6[c]	66	1.0	164	1.4[c]	133	1.3	13	1.1	685	0.8	12
Ovary	F	0.9	549	1.0	16	1.0	63	0.9	40	0.9	195	1.0	311	0.9	150	0.7	12	0.9	954	1.1	30
Endometrium	F	0.8	1,154	1.6[c]	58	1.1	154	0.8	79	1.1	597	1.0	723	0.9	369	0.8	27	0.8	2,003	0.7[c]	38
Breast	F	1.1	3,656	1.1	101	0.9	314	1.0	247	1.1	1,314	1.0	1,734	0.9	913	1.0	85	1.0	5,656	1.0	157
Prostate	M	0.8	1,535	1.2	39	1.1	174	0.9	54	1.1	535	1.0	830	1.0	399	0.8	21	0.6[c]	2,328	0.7[c]	88
All other sites	M	1.1	1,419	1.0	25	1.0	146	1.4[c]	50	1.0	379	1.0	753	1.1	359	0.8	24	1.1	2,543	1.3	110
	F	1.0	1,179	1.0	34	1.1	132	1.1	95	1.0	418	1.0	700	1.1	375	1.4[c]	44	1.1[c]	2,237	1.2	60

[a] *See* text. M=male; F=female.
[b] This group was the referent group.
[c] The 95% CI excludes 1.0.

TABLE 2.—*Summary of findings of cancer risk by religion*

Neoplasm	Sex	Religion	PIR[a]	Confidence interval	PIR adjusted for socioeconomic class[b]	Effect of nativity[c]	PIR adjusted for nativity[d]	Residual effect of religion	If nonc, alternative explanation[e]	If yes: plausibility of ethnicity explanation[f]	Subgroup of neoplasms with extreme risk
Melanoma	M	Mormon	1.5^g	1.1–2.0	1.7^g	No	—	Yes	—	No	Trunk, legs
		Protestant A	1.4^g	1.1–1.8	1.2	No	—	No	Social class	—	—
	F	Eastern Orthodox	0.3^g		1.7	No	—	No	Chance	—	—
Leukemia	F	Protestant A	0.7^g	0.5–1.0	0.6	No	—	Yes	—	No	Acute nonlymphocytic leukemia Chronic lymphocytic leukemia Chronic myelogenous leukemia
Lymphoma	M	Jewish	1.4^g		1.3	Yes	1.5^g	Yes	—	Yes	All except nodular sclerosing and lymphocytic depletion Hodgkin's disease
		Seventh-Day Adventist	1.7^g		1.9	No	— —	Yes	—	No	Nodular/diffuse lymphoma
	F	Jewish	1.5^g	1.3–1.5	1.7	Yes	1.8^g	Yes	—	Yes	All except nodular sclerosing and lymphocytic depletion Hodgkin's disease
		Seventh-Day Adventist	1.7^g	1.1–2.6	1.8	No	—	Yes	—	No	Nodular/diffuse lymphoma
Thyroid	M	Jewish	2.3^g	1.6–3.4	2.3^g	No	—	Yes	—	Yes	All, especially papillary
	F	"	1.8^g	1.4–1.8	1.6^g	No	—	Yes	—	Yes	All
Colon	M	"	1.3^g	1.2–1.4	1.2^g	No	—	No	Social class	—	—
Rectum	F	Mormon	0.6^g	0.3–0.9	0.8	Yes	0.8	No	Social class, birthplace	—	—
Pancreas	M	Jewish	1.3^g	1.1–1.7	1.4^g	Yes	1.2	No	Birthplace, social class	—	—
	F	"	1.4^g	1.1–1.7	1.2	Yes	1.3^g	No	Birthplace, social class	—	—
Bladder	M	"	1.4^g	1.2–1.5	1.4^g	No	—	Yes	—	Yes	Not examined
Lung	M	"	0.7^g	0.6–0.8	0.7^g	No	—	Yes	—	Yes	Squamous
		Seventh-Day Adventist	0.7^g	0.4–1.0	0.5^g	No	—	Yes	—	No	All types
	F	Seventh-Day Adventist	0.4^g	0.2–0.7	0.4^g	No	—	Yes	—	No	" "
		Eastern Orthodox	0.7^g	0.5–1.0	0.6^g	No	—	Yes	—	Yes	" "
Larynx	M	Jewish	0.7^g	0.6–0.9	0.7^g	No	—	Yes	—	Yes	Not examined
		Mormon	0.5^g	0.3–0.9	0.5^g	No	—	Yes	—	No	" "
Oral	M	Jewish	0.4^g	0.3–0.5	0.5^g	No	—	Yes	—	Yes	All squamous
	F	"	0.6^g	0.5–0.8	0.8^g	No	—	Yes	—	Yes	" "
		Protestant C	1.4^g	1.1–1.8	1.1	Yes	1.1	No	Social class, birthplace	—	—
Esophagus	M	Jewish	0.6^g	0.4–0.9	0.3^g	No	—	Yes	—	Yes	Not examined
		Roman Catholic	1.4^g	1.0–2.0	1.1	No	—	No	Social class	—	—
	F	Roman Catholic	1.5^g		1.2	No	—	No	" "	—	—
Stomach	M	Jewish	1.3^g		1.2	Yes	1.1	No	Birthplace	—	—
		Protestant A	0.7^g	0.5–0.9	0.6^g	No	—	Yes	—	No	Fundus Antrim
		Eastern Orthodox	2.8^g	1.8–4.1	2.2^g	Yes	Insufficient data	Yes	—	Yes	Fundus
	F	Jewish	1.4^g	1.2–1.8	1.5^g	Yes	1.4^g	Yes	—	Yes	Fundus Antrim
		Protestant C	1.4^g	1.0–1.8	1.5^g	No	—	Yes	—	No	Fundus
		Roman Catholic	1.4^g	1.1–1.7	1.6^g	No	—	Yes	—	Yes	Fundus
Gallbladder	F	Roman Catholic	1.5^g	1.0–1.3	1.4^g	No	—	Yes	—	Yes	Not examined

TABLE 2.—*Summary of findings of cancer risk by religion (continued)*

Neoplasm	Sex	Religion	PIR[a]	Confidence interval	PIR adjusted for socioeconomic class[b]	Effect of nativity[c]	PIR adjusted for nativity[d]	Residual effect of religion	If none, alternative explanation[e]	If yes: plausibility of ethnicity explanation[f]	Subgroup of neoplasms with extreme risk
Cervix	F	Jewish	0.3[g]	0.3–0.4	0.3[g]	No	—	Yes	—	Yes	" "
		Christian Scientist	1.5[g]	1.0–2.0	1.0	No	—	No	Social class	—	
		Protestant A	0.6[g]	0.4–0.8	0.5[g]	No	—	Yes	—	No	" "
		Protestant C	1.4[g]	1.1–1.7	0.9	Yes	1.2	No	Birthplace, social class	—	
Endometrium	F	Seventh-Day Adventist	1.4[g]	1.1–1.8	1.3[g]	No	—	Yes	—	No	" "
		Eastern Orthodox	0.7[g]	0.5–0.9	0.6[g]	Yes	Insufficient data	Yes	—	Yes	" "
Prostate	M	Roman Catholic	0.6[g]	0.6–0.7	0.6[g]	No	—	Yes	—	Yes	" "
		Eastern Orthodox	0.7[g]	0.6–0.9	0.6[g]	No	—	Yes	—	Yes	" "
All other sites	M	Christian Scientist	1.4[g]	1.0–1.8	0.9	No	—	No	Social class	—	—
		Jehovah's Witnesses	1.4[g]	1.0–1.8	0.9	No	—	No	" "	—	—

[a] Data are from table 1.
[b] Highest and lowest classes are excluded.
[c] The relative risks were <.8 or >1.2 for Europe, or U.S. South or Mountain vs. other birthplace.
[d] Adjustment is within stratum of other birthplace.
[e] Lack of effect is due to a factor other than ethnicity.
[f] Data are from table 3.
[g] The 95% CI excludes 1.0.

TABLE 3.—*Religion by ethnicity (surname), U.S.-born white non-Spanish patients with cancer, all sites, Los Angeles County, 1972–82*

Ethnic group	Sex	Percent of names by religion										
		Jewish	Seventh-Day Adventist	Mormon	Christian Scientist	Protestant A	Protestant B	Protestant C	Jehovah's Witnesses	Roman Catholic	Eastern Orthodox	Total
English	M	37.0	63.2	65.3	63.6	64.8	54.3	71.5	69.7	45.2	51.0	58.7
	F	39.1	56.4	62.5	63.6	62.7	58.3	67.9	60.0	51.8	53.5	58.7
Celtic	M	2.4	9.4	10.4	7.5	12.8	9.0	11.0	5.1	22.2	5.9	12.5
	F	3.1	13.3	12.6	11.5	12.1	10.9	12.1	13.1	18.1	14.0	12.2
German	M	40.1	8.5	6.1	16.0	9.6	16.0	6.9	8.1	10.9	0	13.0
	F	36.0	15.2	7.2	10.9	11.3	12.6	7.4	14.3	10.6	12.8	12.8
Scandinavian	M	7.6	12.3	16.1	6.4	9.2	16.5	7.3	8.1	6.2	13.7	9.1
	F	8.7	10.9	13.8	9.2	9.7	14.4	8.5	4.0	7.5	5.8	9.4
Baltic–Hungarian	M	2.8	1.9	0.7	3.2	1.5	1.1	0.6	3.0	1.9	2.0	1.3
	F	3.2	1.4	0.8	1.0	1.2	0.6	0.8	0.6	1.6	1.2	1.2
Slavic	M	2.8	0	0.2	1.1	0.1	0.5	0.1	0	1.9	2.0	1.0
	F	2.7	0	0.5	0.6	0.2	0.4	0.3	1.7	1.3	0	0.8
Latin–Mediterranean	M	5.0	4.7	1.3	1.6	1.7	2.0	2.5	4.0	10.8	23.5	4.9
	F	5.1	1.9	2.5	3.2	2.2	2.6	2.5	5.1	8.2	10.5	4.1
Other	M	0.9	0	0	0	0.1	0.1	0	0.2	0	0.2	
	F	0.8	0.5	0	0.2	0.1	0.1	0.3	0.6	0.3	2.3	0.3
Not coded	M	1.3	0	0	0.5	0.3	0.5	0.1	2.0	0.8	2.0	0.5
	F	1.3	0.5	0.1	0	0.5	0.2	0.2	0.6	0.6	0	0.5
		No. of patients										
	M	3,811	106	608	187	1,586	2,436	1,553	99	2,355	51	46,730
	F	5,184	211	762	524	2,567	3,456	2,162	175	9,913	86	57,034

indication of whether the confidence interval excludes 1.0. Because of small numbers overall, breast and gallbladder results for males are not presented. Table 2 presents the associations in which we were interested after application of the screening criteria, with indications of whether each result could be plausibly explained by social class, nativity, or ethnic origin. Table 3 provides the ethnic (surname) distributions for all non-Hispanic white patients by religion.

In general, relative risks for members of the Protestant A category seem to be opposite in direction from those of Protestant C. For melanoma in men (high in A) and oral cancer in women (high in C), these trends are explicable on the basis of social class. For cervix cancer, birthplace or social class might explain the high risk in the Protestant C group but not the low risk in the A group. Risk from stomach cancer (high in Protestant C women, low in Protestant A men) and leukemia (high in Protestant A men) cannot be explained by other factors as measured. The tendency is consistent for Protestant A risk levels of cancer of the esophagus, larynx, and oral cavity in women to be higher than those of Protestant B and C women, although none of these differences was individually incompatible with chance.

Cancer in Christian Scientists appears to occur with about the same site distribution as it does in the Protestant B group. An apparent high risk for cervix cancer can be largely explained by differences in social class, as can the slight increase among men for those other cancers not individually specified.

Jehovah's Witnesses, who belong to a strongly evangelical church like those of most Protestant C groups and who therefore also include in their congregations many recent converts to fundamentalism, tend to have a pattern of risk that parallels that of Protestant C groups, although the numbers are admittedly small and the trends compatible with chance. The one finding among them that is statistically significant, an increase among males for all sites not individually examined, appears to be attributable to their lower average social class.

The low rate of melanoma in Eastern Orthodox Christians may either reflect ethnicity or only average social class, as may the apparent high risk from esophagus cancer in Roman Catholic men and women. Eastern Orthodox women do appear to experience a high risk from stomach cancer and a low risk from both endometrial and lung cancer. The high risks of stomach and gallbladder cancers in Roman Catholic women and the low risk of prostate cancer in Roman Catholic men cannot be attributed to social class or nativity.

The most extreme cancer pattern for any Los Angeles religious group in relation to the Protestant B standard is that for Jews. The high risks of pancreas cancer in men and women and of colon cancer in men can be attributed to social class or nativity. The high risk of stomach cancer in men is also explicable on the basis of nativity, but the parallel high risk in women cannot be so explained. Low risks of esophagus, lung, larynx, and oral cancers in men can only partly be explained by social class, but the high risk of bladder cancer in Jewish men is actually opposite in direction to that expected under the presumption of a relationship to cigarette consumption. Cervical cancer occurs one-third as often among Jews as among Protestant B women, even after adjustment for social class and exclusion of the foreign born. Neither the high risk of lymphoma nor that of thyroid cancer, each present in Jewish men and women, could be explained by social class or nativity.

Seventh-Day Adventist men and women also seem to experience a high risk of lymphoma that cannot be explained. Risks from smoking-related sites of cancer are uniformly low in this group, although only lung cancer occurred with sufficient frequency to fulfill all screening criteria. Adventist women have an otherwise unexplained high risk of endometrial cancer, and, although the number permits chance to serve as an explanation, a low risk of cervix cancer. Breast cancer in women and colon cancer in men and women comprised about the same proportion of all cancers as they did among Protestant B church members.

Mormon men also experience a diminished risk for larynx cancer, although risks for other smoking-related sites (and for larynx cancer in women) are unexceptional; esophagus cancer risk even appeared to be slightly increased. Mormon men also seem to get more melanomas than do Protestant B men, a tendency not explained by social class. A slightly low risk from rectal cancer in Mormons can be explained by either social class or birthplace. As with Adventists, female breast cancer and male and female colon cancer risks are unexceptional.

The use of proportional incidence methods in Los Angeles has produced results not completely in agreement with population-based risk estimates for cancer incidence in Mormons in Utah (*5*) or with mortality in Seventh-Day Adventists in California (*6*). Table 4 summarizes a comparison with previous findings in Mormons, and table 5 does likewise for findings in Adventists. Columns 1 and 2 in each table summarize the observed discrepancies. For Mormons in Los Angeles, we were unable to demonstrate the decreased incidence of lung cancer, most other smoking-related cancers, or colorectal cancer that has been shown in Utah Mormons. The original assessment of mortality in Seventh-Day Adventists also showed a strong protective effect operating for each of these same neoplasms; in Los Angeles, only the deficit of lung cancer was apparent in both sexes, although a deficit of other smoking-related cancers was present in women.

DISCUSSION

Of the religious groups described here, there have been previous evaluations of cancer risk in Christian Scientists, Catholics, Protestants, Jews, Mormons, and Adventists.

Analysis of Christian Scientist decedents examined by the coroner in Seattle led to the suggestion that they experienced a deficit of lung cancer (*7*). Because the church discourages smoking, one might anticipate a deficit of cancer at other smoking-related sites as well. Because Christian Scientists are less likely to avail themselves of medical care than others, one might also anticipate less endometrial and more cervical cancer among them, although such a difference could be obscured by differential

TABLE 4.—*Comparisons of Los Angeles County and Utah absolute and proportional estimates of cancer incidence and risk in Mormons*[a,b]

Neoplasm	Sex	PIR	SIR		PIR				
		LA Mormons to Protestant B[c]	Utah Mormons to TNCS[d]	LA total to TNCS[e]	LA total to TNCS[e]	LA Protestant B to TNCS[f]	LA Mormons to TNCS[g]	Utah Mormons to TNCS[h]	Utah non-Mormons to TNCS[i]
Lung	M	0.9	0.4	1.1	0.9	0.8[j]	0.7[j]	0.3[j]	0.5[j]
	F	1.0	0.3	2.1	1.5[j]	1.5[j]	1.4[j]	0.3[j]	0.4[j]
Other smoking	M	0.9	0.7	1.2[j]	1.0	1.0	0.9	0.9	0.7[j]
	F	0.9	0.6	1.5[j]	1.0	1.0	0.9	0.5[j]	0.6[j]
Colorectal	M	0.9	0.6	1.2[j]	0.8[j]	0.9	0.8[j]	0.5[j]	0.5[j]
	F	0.9	0.6	1.1	0.7[j]	0.8[j]	0.7[j]	0.5[j]	0.6[j]
Prostate	M	1.1	1.1	1.2[j]	1.0	1.1	1.2[j]	0.8[j]	0.7[j]
Breast	F	0.9	0.8	1.3[j]	0.9	1.0	0.9	0.7[j]	0.7[j]
All other sites	M	1.1	0.8	1.2[j]	1.2[j]	1.2[j]	1.3[j]	2.0[j]	2.1[j]
	F	1.1	0.8	1.2[j]	1.1	1.1	1.2[j]	1.6[j]	1.6[j]
All sites	M	1.0	0.7	1.2[j]	1.0	1.0	1.0	1.0	1.0
	F	1.0	0.8	1.3[j]	1.0	1.0	1.0	1.0	1.0
No. of patients		2,332	12,175	94,886	94,886	11,171	22,332	12,776	8,113

[a] SIR = standardized incidence ratios; LA = Los Angeles County; TNCS = Third National Cancer Survey; M = male, F = female.

[b] *See* text for methods of computation.

[c] Ratios are for incidence in Mormons and Protestant B >34 yr old in Los Angeles County (1972–81).

[d] Ratios are for incidence in Utah Mormons (1967–75) to whites in the TNCS (1969–71). Original authors judged these findings incompatible with chance.

[e] Ratios are for incidence in whites: Los Angeles County (1972–81) to TNCS (1969–71).

[f] Ratios are for incidence in Protestant B in LA (1972–81) to whites in TNCS (1969–71), both >34 yr.

[g] Ratios are for incidence in LA Mormons (1972–81) to whites in TNCS (1969–71), both >34 yr.

[h] Ratios are for incidence in Utah Mormons (1966–75) to whites in TNCS (1969–71), both >34 yr.

[i] Ratios are for incidence in non-Mormons in Utah (1966–75) to whites in TNCS (1969–71), both >34 yr.

[j] The 95% confidence intervals exclude 1.0.

TABLE 5.—*Comparison of Los Angeles County and California absolute and proportional estimates of cancer incidence, mortality, and risk in Seventh-Day Adventists*[a, b]

		PIR	SMR	SIR	PIR				
Neoplasm	Sex	LA SDA to Protestant B[c]	Cal SDA to U.S. whites-A[d]	LA total to U.S. whites[e]	LA total to U.S. whites[e]	LA Protestant B to U.S. whites[f]	LA SDA to U.S. whites[g]	Cal SDA to U.S. whites[h]	Cal ACS to U.S. whites[i]
Lung	M	0.7[j]	0.1[d]	1.3[j]	1.2[j]	1.1	0.8[j]	0.3[j]	0.9
	F	0.4[j]	0.2[d]	2.1[j]	2.1[j]	2.0[j]	1.0	0.4[j]	0.9
Other smoking	M	0.8[j]	0.4[d]	1.1	1.0	1.0	0.8[j]	0.7[j]	0.8[j]
	F	0.6[j]	0.6[d]	1.1	0.9	0.8[j]	0.5[j]	0.7[j]	0.7[j]
Colorectal	M	0.9	0.6[d]	1.0	0.9	1.0	0.9	1.0	1.1
	F	1.0	0.5[d]	0.8[j]	0.9	0.9	0.9	0.8[j]	1.0
Prostate	M	1.2[j]	0.9	1.2[j]	1.0	1.2[j]	1.5[j]	1.5[j]	1.2[j]
Breast	F	1.1	0.9[d]	1.1	1.1	1.1	1.3[j]	1.4[j]	1.3[j]
All other sites	M	1.2[j]	0.9	1.0	0.9	0.9	1.1	1.5[j]	1.1
	F	1.2[j]	0.8	0.8[j]	0.9	0.9	1.0	1.1	1.0
All sites	M	1.0	0.5[d]	1.1	1.0	1.0	1.0	1.0	1.0
	F	1.0	0.7[d]	1.0	1.0	1.0	1.0	1.0	1.0
No. of patients		528	1,046	94,886	94,886	11,171	528	1,046	4,157

[a] SMR = standardized mortality ratios; SIR = standardized incidence ratios; LA = Los Angeles County; SDA = Seventh-Day Adventists; Cal = California; M = male; F = female.

[b] *See* text for methods of computation.

[c] Ratios are for estimated mortality of Seventh-Day Adventists to Protestant B >34 yr old in Los Angeles County with incidence 1972–81.

[d] Ratios are for mortality of Seventh-Day Adventists in California (1960–71; Adventist Health Study) to mortality of U.S. whites (1960–75), both >34 yr old. Original authors judged this finding incompatible with chance.

[e] Ratios are for mortality in LA non-Spanish whites (1970–81) to U.S. whites (1966 and 1969), both >34 yr old.

[f] Ratios are for estimated mortality of Protestant B in LA with incidence 1972–81 to mortality in U.S. whites (1966 and 1969), both >34 yr.

[g] Ratios are for estimated mortality of Seventh-Day Adventists in LA with incidence 1972–81 to mortality in U.S. whites (1966 and 1969), both >34 yr.

[h] Ratios are for mortality of Seventh-Day Adventists (1960–71; Adventist Health Study) to mortality in U.S. whites (1966 and 1969), both >34 yr old.

[i] Ratios are for mortality of non-Adventist Californians from the American Cancer Society sample (1960–71) to mortality in U.S. whites (1966 and 1969), both >34 yr old.

[j] The 95% confidence intervals exclude 1.0.

education and the apparent propensity of Christian Scientists to use standard routine medical services for everyday problems (*8*). Although all these expectations are fulfilled by trends in our results, the only individual site that passed all screening criteria was the cervix, and the excess risk for that site could be explained by the social class of Christian Scientists in Los Angeles.

Cancer risk in Jews has been studied in New York City (*9-11*), Baltimore (*12*), New York State (*13*), and Israel (*14*). Each of these studies has reproduced the finding of a strikingly low risk of cervical cancer. Most have also found low risk of oral, esophageal, and laryngeal cancer. Whereas each investigator has also found lung cancer risk to be relatively low in Jewish men, each has found it to be relatively high in Jewish women. We observed the first but not the second of these differences, possibly because of changes in the smoking practices of recent cohorts of non-Jewish women.

If these results for respiratory and upper gastrointestinal cancer sites reflect Jewish patterns of smoking and drinking, the observed patterns of bladder and pancreas cancer occurrence do not. MacMahon (*9*) and Greenwald et al. (*13*) reported an excess of pancreas cancer in Jews. As previously reported (*15*), we confirmed such an excess in Los Angeles but now find it to be explicable on the basis of social class and birthplace. Seidman (*11*) found a deficit of bladder cancer in Jewish men. However, we now find an anomalous high risk from bladder cancer in Jewish men that cannot be otherwise explained. We also confirm the high stomach cancer rates found by those who conducted the only previous study of Jews that was based on incidence (*13*), rather than mortality, and conclude that, at least in women, this finding cannot be fully explained by nativity. Perhaps the most interesting and inexplicable findings in Jews and in our entire study are the excess risks for both sexes of lymphomas (both Hodgkin's and non-Hodgkin's) and thyroid cancer (especially papillary adenocarcinoma). The former finding has also been observed in previous descriptive studies (*9, 11, 12*) and in case–control studies (*16*), and that for cancer of the thyroid was noted in Los Angeles (*17*) and in 1 other descriptive study (*11*).

Whereas relative abstention from heavy smoking, heavy drinking, and promiscuous sexual activity on the part of Jewish men could provide protection among Jews from upper gastrointestinal respiratory and cervical cancers, the observed high risks are not easy for us to explain after ruling out social class and nativity. Inherited factors are consistent with (but not particularly attractive explanations of) the high stomach cancer and lymphoma risk, which have been repeatedly observed. Alternatively, either these or the excess occurrence of thyroid or bladder cancer could plausibly derive from some habituation, dietary item, or medical practice determined by either educational or cultural factors.

Most of the above investigations (*9–12*) also compared the pattern of cancer in Catholics to that in Protestants. In no study were these patterns different, although a higher risk from prostate (*11*) and esophagus (*12*) cancers in Catholic men has been previously observed; gallbladder cancers were always too few in number to warrant special mention. Whereas individual Protestant denominations have not been separately examined before, white Protestant clergy have been seen to be at low risk of stomach, rectum, lung, and bladder cancers relative to the population at large (*18*). It seems quite likely that for Catholics and Protestants (including Eastern Orthodox Christians and Jehovah's Witnesses) the variations we see represent not the effects of religious beliefs themselves but complex mixtures of socioeconomic and other cultural determinants.

The differences between our observations of Mormons and Adventists and those of previous observers may truly represent differences in the pattern of risk between geographically separate coreligionist communities. Alternatively, they may represent differences between methods of identifying cases, between standards used for comparison, or between methods of analysis. In tables 4 and 5, columns 1 and 2 contrast the original findings to ours based on proportional incidence for each site of interest. Columns 3, 4, and 5 provide a direct comparison between Los Angeles overall white incidence and the original incidence standard, the analogous PIR during the same period, and the PIR for the actual Los Angeles standard, the Protestant B group, in comparison with the same original standard. In columns 6 and 7, the 2 coreligionist case groups are each compared against the same original standard, and, in the final column, an identical calculation is provided for each of the second, "internal" control groups originally reported (Utah non-Mormons and American Cancer Society non-Adventists), who were identified according to the same methods as were the originally reported cases.

Overall, the all-site cancer risk in Los Angeles during the period of our study was 20–30% higher than that recorded in the Third National Cancer Survey, which was used as the incidence standard for the Utah study. When we take that difference into account, the comparison of estimated risks by site between the 2 standard populations gives uniform results whether incidence or proportional incidence methods are used, or whether the entire Los Angeles group or the Protestant B subgroup standard is used. When each of the 2 coreligionist groups is compared by proportional incidence to the same Third National Cancer Survey standard, a true disparity is apparent between them, such that lung cancer, colorectal cancer, and, in females, other smoking-related cancers are less common in Mormons in Utah than in those in Los Angeles. Exactly the same pattern of deficiencies is present among Utah non-Mormons, whether measured as in the original paper with a comparison of incidences or, as in column 8, with proportional methods. This suggests that the differences between Utah and Los Angeles lie not in the choice of standard, nor in the difference in analytic methodology, nor even largely in religious practice, but in some cultural or environmental difference not between Mormons and non-Mormons but between the populations of Utah and Los Angeles or, to be complete, possibly in some aspect of the Utah case-ascertainment process. It does seem likely that the originally observed deficit in cancers of the respiratory and upper gastrointestinal tract in Utah are attributable to a lower prevalence of smoking, and, therefore, we postulate that Los Angeles Mormons have more smoking experience as a group than either Utah Mormons or non-Mormons. Mortality studies in California Mormons appear to have reproduced the finding of low risk in Utah coreligionists (*19*), but the uniformity of the observed mortality deficit suggests the strong possibility of incomplete ascertainment. Nonsmoking is especially plausible as an explanation for true Utah deficits because comparisons between groups of Utah Mormons subdivided on the basis of the degree of religious adherence have shown the expected gradients for these same sites (*20, 21*). No such gradients confirm the Utah Mormon deficits of colorectal cancer, breast cancer, or any of the other sites reported to be low in Utah but not confirmed here.

Comparison of the original standard mortality of Seventh-Day Adventists with the Los Angeles population and its standard (columns 3, 4, and 5 of table 5) also show essentially no differences between the patterns of cancer in the 3 populations. In a proportional comparison of the original group of California Adventists to the original mortality standard (column 7), the original, unlike the non-Adventist internal comparison group (column 8), shows the familiar dramatic deficiency of respiratory cancer but not the deficit of colorectal cancer. This inconsistency with the original direct comparison can be explained only if a deficiency of colorectal cancer were accompanied by a quantitatively similar proportional deficiency in the frequency of all cancers. A similar comparison of Los Angeles Adventists with the original standard shows a nearly identical pattern, with the exception that the more contemporary urban Los Angeles Adventists, who should be expected under the null hypothesis to show an excess mortality from respiratory cancer in comparison with the earlier comparison cohort, do not. The lack of such an excess should be interpreted as an actual deficiency, as seen in the more appropriate comparison between contemporary co-resident groups in column 1.

The originally reported deficiency of colorectal cancer deaths in Adventists could reflect either decreased incidence or a decreased ratio of mortality to incidence in Adventists. Failure to confirm it by a proportional analysis of incidence means either that the original deficit was a mortality artifact produced by earlier diagnosis, better treatment, or less complete cancer death registration among Adventists, or that the actual incidence is lower, but to roughly the same degree that all cancer incidence is lower among Adventists. Although neither of these alternatives can be definitely ruled out and observations supporting the latter explanation have been presented (*22, 23*), we believe that the apparent deficiency of colorectal cancer is likely to reflect a measurement artifact for several reasons. The proportional analysis of incidence did show lower levels at various smoking-related sites, some of which were no more profoundly reduced than colorectal cancer in the original mortality analysis, and yet it showed no reduction in bowel cancer even when colon cancer was examined alone. The lack of any difference between the proportional pattern of cancer in the original Adventist cohort and that in urban Los Angeles Adventists does not reflect the probable difference in degree of adherence to vegetarianism in the 2 populations. Although in investigating the small numbers of Danish Adventists, Jensen (*22*) found a deficiency of colon cancer incidence, his study was small and inconsistent with that in California because he observed no deficit of rectal cancer and little overall deficit of colorectal cancer. Results of a cohort study of Dutch Adventists revealed uniform deficiency of death from almost all causes (*23*), which again suggests incomplete ascertainment. Breast cancer has been shown to be less commonly fatal in Adventists (*24*), who have ready access to medical care of high quality. Higher survival in such a group would produce an apparent reduction in mortality rate. A comparison of colorectal cancer mortality in Adventist physicians compared with other Southern California physicians, who presumably have access to care of an equal standard as well as being precisely comparable in social class and in level of daily activity, has shown no differential colon cancer mortality (*25*). Vegetarianism in other Western groups has not been shown to be related to such a deficit in colorectal cancer incidence (*26*). Finally, although the vegetarianism in Adventists has been well-documented (*27*), it does not seem to be related to colon cancer in Adventist individuals (*25*). In summary, although it is plausible that Adventists experience a lower incidence of colorectal cancer, the weight of mixed evidence actually may be against a link between this specific life-style and colon cancer, and it certainly should not be used instead of data from individuals as supporting evidence for dietary recommendations, as it often has been (*28*).

Of more interest than colon cancer in Adventists should be the apparent high risk of lymphoma, predominately non-Hodgkin's lymphoma, in Adventist men and women. Like Jews, Adventists smoke fewer cigarettes and have a relatively high median education, a high level of use of medical care, a small family size, a pattern of social stability, and presumably a relatively well-protected childhood. Although we may be tempted to attribute the lymphoma risk to one of these characteristics, intensive scrutiny would probably reveal many other similarities between these 2 religious groups and to presume that any specific characteristic is responsible for any specific parallel in cancer incidence would be to do so on the basis of incomplete information.

Explanation of the high melanoma risk in Mormon men is not any easier because it cannot be attributed to birthplace, ethnicity, or social class. One can only speculate that Mormon boys, who are active in outdoor activity groups, such as Boy Scouts, are more exposed to the sun.

In fact, the principal obstacle between the observation of a particular cancer pattern of a religious community and the construction of a credible hypothesis in explanation of the pattern is our ignorance of the true pattern of life-style within any religious community in comparison with that of others. Religious belief may clearly result in relationships and practices which bear on cancer risk (*29*), but the choice of religious affiliation may just as clearly result from historical or cultural circumstances that also bear on cancer risk. Other than the familiar relationship between religion, smoking, and the incidence of smoking-related cancers, it is not possible at this time for us to identify even with reasonable certainty any truly or even presumptively religious determinants of cancer occurrence. If religious denominations are viewed as historical and cultural as well as theological entities, the resulting broader search for explanations of unusual cancer patterns may still produce results.

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SESSION VI

Chemoprevention Trials

Rationale and Design of Cancer Chemoprevention Studies in Seattle [1]

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ABSTRACT—Three cancer prevention trials are currently in their early phases at The Fred Hutchinson Cancer Research Center, the University of Washington School of Public Health and Community Medicine, and the Swedish Hospital. All 3 studies are randomized and placebo controlled. One large-scale study involves the daily administration of retinoids to persons with asbestos-related lung disease in an attempt toward reduction of their high risk for bronchogenic carcinomas and mesotheliomas. A second study involves administration of the same agents to long-term heavy smokers; a substantial feasibility and toxicity pilot study will precede a full-scale prevention trial. In the third trial, folic acid administration is evaluated in relation to the progression and regression of cervical dysplasia among women with abnormal Pap smears. We report here the rationale and the design for these 3 studies.—Natl Cancer Inst Monogr 69: 249-258, 1985.

The striking variations of site-specific cancer incidence rates among geographic areas and the tendency of cancer incidence rates among migrants to gravitate toward prevailing rates in their new location (*1*) suggest an important role for life-style factors in cancer etiology. Well-known cancer risk factors, such as cigarette smoking habits, provide an explanation for a portion of cancer rate variations, but much remains to be explained. It is natural that cancer researchers focus on dietary habits as a potentially important component of cancer risk determination. Doll and Peto (*2*), in their review of the causes of cancer, suggest that it may be possible to reduce cancer mortality rates in the U.S. by as much as 35% by "practicable dietary means." However, as these authors acknowledge, this estimate is by no means reliable at this time.

Dietary practices could relate to cancer occurrence in either a causative or a preventive manner. For example, as detailed in a recent article by Ames (*3*), the human diet contains both a variety of natural mutagens and carcinogens as well as many antimutagens and anticarcinogens. Dietary interventions may then be entertained that reduce the intake of potentially carcinogenic substances or that increase the intake of substances that may inhibit cancer cell initiation or promotion. Of particular interest in relation to cancer prevention among persons who are currently at high risk for cancer is the identification of interventions that inhibit the later stages of neoplastic transformation. In view of the long latent period associated with the appearance of many cancers, it is reasonable for one to suppose that high-risk individuals possess partially transformed cells which are at risk for subsequent transformation into malignant cells, unless retarded by some late-stage intervention.

From some points of view, it is premature for investigators to embark on large-scale dietary intervention trials: The mechanism of action of apparent carcinogens and anticarcinogens in the diet is not well understood; epidemiologic studies of dietary intakes or serum nutrient levels are not specific enough to isolate clearly the most promising agents for dietary intervention; and human data on the side effects of long-term administration of potential anticarcinogens are limited. On the other side of the argument, however, the potential pay-off for cancer reduction (or control) is great. We need not understand the mechanism of action for a preventive agent (or program) to benefit from its application; some possible dietary interventions cannot even be evaluated by means of observational studies; animal intervention studies provide motivation toward the dietary intervention and chemoprevention concept; and, finally, the process of conducting human prevention trials may yield extremely useful information for the planning and conduct of subsequent intervention studies even if the primary goal of the intervention is not realized.

The subsequent sections document some aspects of our struggle with the limitations of currently available data with respect to the planning of 3 chemoprevention studies. Despite the many unknowns, carefully controlled trials seem to us to have merit at this time. These trials take place in the context of a Cancer Control Research Unit funded by the Division of Cancer Prevention and Control of the National Cancer Institute.

ABBREVIATIONS: 13-cRA = 13-*cis*-retinoic acid; CIN I = mild dysplasia; CIN II = moderate dysplasia; CIN III or CIS = severe dysplasia; 4-oxo-cRA = 4-oxo-retinoic acid.

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STUDY RATIONALE

Lung Cancer Prevention by Use of Retinoids Among Persons With Asbestos-related Lung Disease

Lung cancer is the leading cause of death from cancer in the U.S., with approximately 110,000 lung cancer deaths per year (*4*). It is unique in that its primary causative agent, cigarette smoking, has been identified (*5, 6*). Nevertheless, treatment results for lung cancer are disappointing and 5-year survival remains about 10%.

Persons heavily exposed to respirable fibers of asbestos also have a highly elevated lung cancer risk (*7, 8*). Moreover, the relative risk from the combination of cigarette smoking and asbestos fiber exposures appears to be approximately the product of the 2 relative risks. In the Hammond-Selikoff studies of various groups of insulation and asbestos workers, 83% of the 17,800 subjects are or were smokers. Under specified exposure definitions, smoking alone was estimated to enhance lung cancer risk by a factor of 10, asbestos exposure alone by a factor of 5, and the combination by a factor of about 50. The latent period following asbestos exposure appears to be at least 15 years and may be 30 years or more. For mesothelioma, which is not smoking related, the latent periods may be even longer. An estimated 4 million workers were exposed to significant amounts of asbestos in shipyards and related activities during the period of World War II. Nicholson et al. (*9*) have predicted that those already exposed to asbestos in various ways will suffer asbestos-related cancer deaths at a rate of 8,000–10,000/year to the end of the century. According to Peto and associates (*10*) and Schneiderman et al. (*11*), mesothelioma risk may depend on approximately the third power of elapsed time since first exposure to asbestos. If this extrapolation is correct, mesothelioma rates may rise precipitously in the decades ahead. These considerations point to the importance of cancer control strategies that interrupt the late stages of bronchogenic carcinoma and mesothelioma cell formation and proliferation during the long latencies for these tumors.

Workers and former workers who already have a diagnosis of asbestosis are at a particularly elevated risk for bronchogenic carcinoma and mesothelioma. For example, in a study in the United Kingdom of 665 men certified as having asbestosis (only 5% of whom had never smoked), 66 cases of lung cancer and 16 cases of mesothelioma arose in 2,185 person-years of follow-up (*12*). Thus a particularly useful preventive trial may be undertaken if a sufficient number of subjects with asbestosis can be enrolled.

Let us consider possible cancer intervention strategies for this group of extremely high-risk individuals. Certainly, smoking cessation should be encouraged. However, additional strategies are clearly needed because individuals with substantial histories of asbestos and cigarette smoke exposure are at much increased risk regardless of their future cigarette smoke and asbestos exposures. Furthermore, many high-risk individuals will be unable or unwilling to give up cigarette smoking.

Vitamin A and its family of synthetic and naturally occurring analogues, the retinoids, have attracted wide interest as possible chemopreventive agents (*13–15*). The effects of retinoids on the development of pulmonary neoplasms have been examined in several studies with animals. Saffiotti and co-workers (*16*) showed that retinyl palmitate administered 7 days after carcinogen administration can inhibit the development of squamous cell carcinomas in Syrian golden hamsters. Port et al. (*17*) reported the prevention of lung cancer in hamsters treated with the synthetic retinoid, 13-cRA. Mossman and associates (*18*) demonstrated that retinyl methyl ester inhibits the metaplastic transformation that cultured hamster tracheal cells undergo when exposed to amosite or crocidolite forms of asbestos. Lasnitzki and Bollag (*19*) have recently shown that the synthetic retinoid etretinate can inhibit or prevent the increase in mitotic activity that occurs when mouse lung or rat trachea is exposed to cigarette smoke condensate. In a study of the effect of early versus late and short- versus long-term exposure to retinyl acetate in relation to the development of chemically induced breast cancer in rats, McCormick et al. (*20*) found that the chemopreventive effect of the retinoid was greatest if administered prior to the carcinogen, but much of the effect remained even when retinyl acetate was delayed until 12 weeks after carcinogen exposure.

In humans, epidemiologic cohort studies indicate an inverse association between indices of dietary intake of vitamin A and subsequent lung cancer incidence (*21, 22*). For example Bjelke (*21*) reported an estimated relative risk of 2.6 for persons with low (<5) versus high (≥5) values for a vitamin A intake index. However, one would find it difficult to utilize these findings in the design of an intervention study for several reasons. Firstly, the correlation is high among dietary intakes of several different classes of nutrients. Secondly, much uncertainty exists about the role of compounds within each class; in the case of vitamin A, the provitamin A beta-carotene constitutes a major component of the vitamin A dietary intake. Thirdly, the difficulties in dietary assessment by way of recall are well known. All these problems limit the potential of dietary surveys to yield specific input to chemoprevention study design.

Serum nutrient level studies suggest elevated lung cancer incidence among subjects with relatively low blood retinol and blood beta-carotene levels. Most such studies have involved the use of diagnostic serum samples from patients with lung cancer, but the possibility that the presence of the disease or its treatment affect serum nutrient levels is left open. However, blood retinol levels as obtained from prediagnostic stored serum was used in 3 small prospective studies (*23–25*). These studies indicate elevated overall cancer incidence among persons with low blood retinol levels, but none of the 3 studies was large enough to yield specific results for lung cancer or to distinguish retinol levels clearly from levels of other nutrients, such as beta-carotene, alpha-tocopherol, and selenium, as indicators of cancer risk. For example, the cancer incidence among persons in the lowest quartile of serum retinol level is estimated to be 2.2 times that in the highest quartile in (*23*). Most importantly, however, an inverse relationship between blood retinol level and cancer risk is of limited usefulness for cancer control purposes because dietary intake of retinol and beta-carotene (*12*) evidently is virtually unrelated to blood retinol level except for patients in regions of the world with gross deficiency of vitamin A intake. In sum, the external determinants of blood retinol level that may relate to cancer risk have yet to be identified.

Clinical studies have demonstrated an effect of retinoids on precancerous lesions (*26*). Of particular interest, Gouveia et al. (*27*) reported that smokers experience a decrease in the degree of bronchial metaplasia following treatment with the synthetic aromatic retinoid, etretinate.

Finally, the literature is extensive on the ability of retinoids to suppress the development of cells of malignant phenotype in vitro (*28, 29*). In certain specialized systems it has been shown that retinoids can exert effects on fully transformed neoplastic cells leading to a suppression of proliferation or to terminal differentiation with non-neoplastic phenotypes (*29, 30*).

Taken together, these diverse studies suggest a great potential for the use of retinoids in the prevention of lung cancer among persons who have substantial exposures to cigarette smoke and asbestos fibers. However, the results of such research give little guidance for the choice of retinoid, let alone the dose and schedule for any given retinoid. Some of our thoughts with respect to the choice of retinoid will be given here. The issue of dose and schedule will be taken up in the section on study design.

Retinol has been available as a dietary supplement for many years. Orally administered retinol is esterified in the small bowel with long-chain fatty acids and is transported to the bloodstream by way of the lymphatics. These retinyl esters are taken up by the liver and stored in hepatocytes. When mobilized, the retinyl esters are deconjugated and transported in the plasma bound to a carrier protein, retinol-binding protein. The rate of mobilization of retinol from the liver is largely independent of the amount stored in the liver (*31*). Dietary intake of retinol will correct a low (or borderline low) blood retinol concentration. In addition to having little effect on carrier-bound retinol levels, high doses of retinol present a dose-related risk of hepatic toxicity as the storage capacity of the liver is exceeded. Thus retinol must be administered at a sufficiently low and frequent schedule to avoid liver toxicity, correct any retinol deficiency, and offer the possibility of exposing peripheral tissues to increased retinoid concentration by means other than carrier-bound retinol, e.g., in the form of retinyl palmitate which appears in the plasma in high concentrations after the administration of oral retinol.

The tight regulation by the liver of plasma retinol concentration suggests that a chemopreventive retinoid strategy should not depend wholly on increased retinol intake. In contrast to retinol, both *trans*- and *cis*-retinoid acid are absorbed directly through the portal system, do not generally accumulate in the liver or other tissues, and appear in the plasma after oral administration. Oxidation of retinol and retinal to retinoic acid is irreversible. Animals provided with retinoic acid as their only source of retinoids will retain normal cellular differentiation and growth rate but will become blind and sterile because retinal is essential for visual function, and retinal or retinol, or both, are needed for the normal function of the reproductive system (*32*). As mentioned above, 13 *cis*-retinoic acid has been shown to prevent lung cancer in animals. Clinical studies have demonstrated activity of 13-cRA against squamous cell cancers and preneoplastic lesions (*33*). These considerations and the experience of one of us (G. E. Goodman) with the pharmacokinetics of 13-cRA make it an attractive choice as a primary chemopreventive agent. However, potential side effects associated with long-term 13-cRA administration may limit the feasibility of this approach among relatively healthy persons.

Other retinoids, including etretinate, which also have in vitro activity were considered as potential chemopreventive agents. It is unclear whether etretinate will ever be approved for clinical use in this country in view of preliminary reports of unfavorable pharmacokinetic parameters and of teratogenic effects in animals.

The provitamin A beta-carotene was also considered in this context. There are a number of attractive features to the use of beta-carotene: Carotenoids are free-radical traps and remarkably efficient quenchers of singlet oxygen (*3*). The inverse correlation between dietary vitamin A indices and cancer incidence in the epidemiologic cohort studies mentioned above may well reflect a dependence of cancer risk on beta-carotene intake. Though careful study does not seem to have taken place, conventional wisdom (*32*) holds that excessive intake of beta-carotene results only in a benign yellow discoloration of the skin. On the other side of the argument, beta-carotene intake is largely uncorrelated with blood retinol levels because beta-carotene oxidized to retinal and subsequently reduced to retinol is regulated by the liver in the manner described above. Beta-carotene intake apparently does relate directly to beta-carotene level in the serum but few have attempted to identify a role for serum beta-carotene as a predictor of subsequent cancer risk in a manner that controls for serum retinol level. Most importantly, in contrast to the retinoids, to date few experimental in vitro or in vivo data document a cancer preventive activity for beta-carotene.

Despite both the lack of experimental data and the absence of human phase I toxicity trials with beta-carotene, we appreciate its attractive features for immediate use in large-scale human prevention efforts. Our decision, instead, to use a combination of low doses of 13-cRA and retinol stems partly from an overview of the chemoprevention effort in humans. Chemopreventive studies incorporating the use of beta-carotene are already under way or soon will be among diverse target populations (including the Harvard study of U.S. physicians and the esophageal cancer study in China described by Dr. Blot at this Symposium). In view of the overall potential of cancer chemoprevention, the current lack of knowledge as to which agents or doses are most promising, and the likely impatience of the general populace for early application of the cancer chemoprevention concept, it seems prudent that various potential cancer chemopreventive agents be evaluated in a variety of settings.

A trial with persons who have asbestos-related lung disease may provide a particularly suitable context in which one can evaluate the chemopreventive activity of 13-cRA because minor side effects may be acceptable to such subjects in view of their extremely high risk for bronchogenic carcinoma and for mesothelioma. Furthermore, most potential subjects are already under medical observation, possibly enhancing compliance and side effect monitoring.

Chemoprevention of Lung Cancer Among Long-term Heavy Cigarette Smokers

Approximately 95% of all lung cancer deaths (≃110,000/yr) in the U.S. have been attributed to cigarette smoking. Moreover, the number of lung cancer deaths attributable to smoking in the U.S. is increasing by about 4,000/year (*2*), and lung cancer is becoming a worldwide epidemic. As mentioned above, the long latent periods associated with this disease provide an opportunity for cancer control among smokers. Smoking cessation efforts are being vigorously encouraged, including those within our Cancer Control Research Unit, but they have had limited success. Those who are able to stop smoking will retain an elevated lung cancer risk for a number of years following cessation (*34*). Thus additional strategies for lung cancer avoidance are needed.

The potential of retinoids for the chemoprevention of lung cancer has been discussed above. An important difference between the use of retinoids in a trial of long-term heavy smokers and use in a trial of persons with asbestos-related lung disease is that the lung cancer relative risk (compared with unexposed persons) in the former group may average as much as 10, whereas in the latter group it may be 50 or more. The long-term heavy smoker, even though at increased risk for lung cancer and a range of other serious diseases may be less willing to tolerate the mild side effects that accompany administration of 13-cRA or to comply with study requirements. As elaborated below, a full-scale prevention trial with 13-cRA or other chemopreventive agent will require substantial sample sizes and sustained follow-up.

For these reasons, our current plans (and funding) in this context are centered on a 3-year pilot study during which we intend to assess the (relatively) long-term side effects associated with 13-cRA, with retinol, and with their combination. Equally important is that with this pilot study we will evaluate subject compliance in taking the chemopreventive agents, in reporting any side effects, and in meeting follow-up examination requirements. Depending on the results of this pilot study, we intend that a full-scale study ensue, using the subjects enrolled in certain arms of the pilot study as a vanguard group for the full trial and possibly incorporating additional chemopreventive agents according to new developments in the interim.

Chemoprevention of Cervical Cancer Among Women With Mild or Moderate Dysplasia

Cervical cancer constitutes about 1.5% of all U.S. cancer deaths (*2*) and a greater fraction (≃3%) of total cancer incidence. Cervical cancer incidence and mortality are much higher in many other parts of the world. Histologic, cytochemical, cytogenetic, and epidemiologic evidence strongly suggests that cervical dysplasia and carcinoma-in-situ are precursors of invasive cervical cancer (*35*). In fact, dysplasia appears to be part of a stepwise process that proceeds from normal epithelium to CIN I, to CIN II, to CIN III or CIS, to invasive cervical cancer. Because the cervix is easily visualized and the precancerous condition is well-documented, this disease offers unique opportunities for intervention studies.

Current standard community care for CIN I and II includes Pap smear and colposcopy every 3 months, or cryocautery laser treatment and Pap smear every 3–6 months, or cone biopsy with yearly Pap smears. Following cryocautery, the squamocolumnar junction, where most cervical cancers develop, often moves up into the endocervical canal out of the range of the colposcope. This makes follow-up of subsequent abnormal Pap smears impossible without cone biopsy. Complications associated with cone biopsy include risks of anesthesia, bleeding, and infection, as well as possible premature labor in subsequent pregnancy. A successful chemopreventive strategy would reduce the complications of treatment and the cost of management of patients with dysplasia.

Under the stepwise development of cervical cancer given above, frequencies and rates of progression from CIN I to CIN II and from CIN II to CIN III or CIS are relevant outcome measures in the evaluation of a cervical cancer chemopreventive strategy. Such progression, without biopsy, has been reported (*36*) to take averages of 58 months (CIN I to CIS) and 38 months (CIN II to CIS), respectively, so that a long-term follow-up study is necessary for an evaluation of progression. Progression, in the absence of intervention, is not inevitable. In fact, rates of regression from dysplasia to normal epithelium are reportedly in the range of 32–54% and usually occur within 1 year (*37–39*). Such regression may be hastened by cervical biopsy inasmuch as residual dysplastic tissue may be destroyed by the inflammatory response to cervical biopsy. The ability to monitor progression and regression through the premalignant stages of this disease is an important advantage in the development of an efficient chemopreventive trial.

Well-known risk factors for cervical dysplasia and invasive cervical cancer include age at first intercourse and number of sexual partners. Other potential risk factors include contraceptive practices and cervical infections. In particular, herpes genitalis has been associated with cervical dysplasia and cancer in a number of studies (*40*), and both *Chlamydia trachomatis* and condylomata acuminata have been associated with cervical dysplasia (*41*). Recently, nutritional factors have been reported to be associated with dysplasia. Patients with dysplasia had lower dietary intakes of total vitamin A and beta-carotene and possibly of ascorbic acid as well than did a comparison group (*42, 43*).

Folic acid has long been recognized as an inhibitor of tumor growth. Early studies by Leuchtenberger and associates (*44*) showed inhibition of spontaneous breast tumors in mice. More recently, Rogers and Newberne (*45*) showed that diets deficient in lipotropes (folate, methionine, and choline) and high in fat enhance chemical hepatocarcinogenesis in rats.

In a randomized trial by Butterworth et al. (*46*), 87 women with CIN I or CIN II, diagnosed by cervical Pap smear and with a history of at least 6 months of oral contraceptive use, received either oral folic acid (10 mg) or ascorbic acid (10 mg) on a daily basis for a 3-month period under double-blind conditions. Cervical biopsies of abnormal areas were obtained at the end of the 3-month period. The mean biopsy dysplasia score and final versus initial cytology score were significantly better ($P<.05$) in the group treated with folate than with ascorbic acid. No carcinoma-in-situ was detected in the former group compared with 4 cases in those women given ascorbic acid. This study indicates that oral folate supplementation may prevent the progression of cervical dysplasia or promote regression to normalcy. Butterworth et al. postulated that prolonged exposure to contraceptive steroids might have altered folate metabolism making the target tissue more susceptible to malignant transformation.

Several motivations promote consideration of a further randomized intervention trial of folic acid. The study by Butterworth and associates did not include initial biopsies; thus the cases of carcinoma-in-situ diagnosed in the women given ascorbic acid may well have been present initially, in view of the usual time course of progression (*36*). Their study was restricted to current oral contraceptive users, but corresponding results for nonusers would also be interesting. Comparisons between the 2 groups were not standardized for dietary retinol and beta-carotene, for vaginal infection, or for other risk factors for progression. Finally, only 47 of the 87 women in the trial completed the protocol and were included in the analysis; thus serious bias in the reported results is possible.

The concept of localized nutrient deficiency provides rationale for a folic acid intervention study. Whitehead et al. (*47*) observed megaloblastic features in cervical epithelial cells in the absence of systemic vitamin deficiency in a group of women using oral contraceptive steroids. The megaloblastic features disappeared when the women were given supplemental folic acid.

Retinoids were also considered as potential chemopreventive agents in this context. In view of side effects associated with oral 13-cRA and the positive report with folic acid (*46*) just discussed, we thought it reasonable to prefer oral folic acid at this time. Also, significant side effects (55% with vaginal toxicity) have been reported in the topical application of *β-trans*-retinoic acid to the cervix (*48*).

Ascorbic acid may merit consideration for cervical cancer intervention in view of its antioxidant and anticarcinogenic properties (*3*). Additional epidemiologic study and study of serum levels of this vitamin in relation to dysplasia and cervical cancer logically might precede its use in an intervention study.

The design of a cervical cancer intervention study that involved daily oral folic acid is described in the latter part of the next section.

STUDY DESIGN

Lung Cancer Chemoprevention With Use of Retinoids Among Persons With Asbestos-related Lung Disease

The rationale for a study of 13 *cis*-retinoic acid and retinol to prevent bronchogenic carcinoma and mesothelioma among persons with asbestos-related lung disease was described above. The following paragraphs describe some details of the design of this intervention study.

Eligibility is restricted to persons of age 45 years or older with at least 10 years since first exposure to asbestos and with evidence of one or more of the following signs: irregular small opacities consistent with pulmonary interstitial fibrosis on x ray; pleural plaques or pleural thickening on x ray; or restrictive changes in the lung on clinical and spirometric examinations. Potential subjects will be excluded on the basis of a history of cirrhosis or hepatitis within the past year; ingestion of 10,000 IU or more of vitamin A supplement daily; or a diagnosis of malignant neoplasm, other than skin cancer, within the last 5 years. We have identified several sources of subjects with asbestos-related lung disease in Washington, Oregon, and California, including state and federal worker compensation systems, the U.S. Navy Asbestos Medical Surveillance Program, longshoremen and harbor workers compensation records, and private physicians treating respiratory diseases. These sources have agreed to make the first contacts, using an explanatory letter we have prepared; the names of persons interested in participation are forwarded to us. In a small pilot study, 54 (60%) of 90 eligible persons contacted indicated a willingness to participate.

Prior to randomization, subjects must consent to the study; provide asbestos exposure, smoking, and dietary histories; and submit to blood drawing for determinations of the levels of retinol, beta-carotene, 13-cRA, 4-oxo-cRA, triglycerides, and cholesterol. Subjects will be assigned to 1 of 4 strata depending on smoking history (current smokers and those who quit after learning of lung problems vs. all others) and years since first exposure to asbestos (10–40 vs. more than 40 yr). Subjects will then be randomized to receive either placebos or a combination of 20 mg 13-cRA/day plus 25,000 IU retinol/day in a double-blind fashion.

Before going into other aspects of the study design, some considerations related to these dose levels of 13-cRA and retinol will be discussed. In fact, essentially no information is available on the side effects associated with long-term (e.g., 5 yr) use of these agents. Short-term phase I-II trials (*33, 49*) among cancer patients all use relatively high doses, mostly greater than $1\ \mathrm{mg \cdot kg^{-1}}$ body weight$\cdot$day^{-1} (70 mg/day for a 154-pound individual). Patients in these studies frequently developed severe but reversible side effects including dermatitis, emotional lability, and headaches. Extremely high doses of 13-cRA and other retinoids have been associated with potential carcinogenic effects in animal studies (*50*). Some have given 13-cRA in moderate to high doses (0.1–3 mg/kg) to patients with various keratinizing skin diseases and acne for longer periods. Symptomatic side effects have been limited mainly to the skin with erythema, scaling, and cheilosis. Dose reduction leads to prompt resolution of these dermatologic side effects. Doses in the range of 3 mg/kg for 2 years have been associated with bony hyperstosis (*51*) and hypertriglyceridemia (*52, 53*). Because hypertriglyceridemia has also been reported at doses less than 1 mg/kg, plasma triglyceride concentrations in a long-term trial should be monitored. Though it is difficult for one to extrapolate dermatologic dose effects from studies on patients with acne, it is worth noting that in a recent study (*54*) on low-dose (0.1, 0.5, and 1 mg/kg) use of 13-cRA in patients with severe acne, cheilitis occurred in nearly all the patients, and facial dermatitis, epistaxis, and desquamation were also fairly common. The incidence of these side effects were not highly dose dependent within the range examined. However, the drug schedule needed to be altered in only 3 of 76 patients.

These results suggest that some side effects can be expected at a dose level of 20 mg/day. We anticipate that some degree of dermatologic discomfort will be tolerable to subjects with asbestos-related lung disease. The side effects in question will occur with some frequency in the placebo group, so we hope that the double-blind protocol can be retained. It is natural that we prefer the largest dose of 13-cRA that will be well tolerated (and will not interfere with compliance or blindness) in view of dose-related results on the chemopreventive efficacy of 13-cRA (*17*) and other retinoids. It would be a pity if a long-term study were done that would be inconclusive because of a suboptimal dose.

Pharmacokinetic aspects of 13-cRA in humans have been reported elsewhere by Goodman et al. (*55*).

High-dose oral retinol toxicity has also been studied in a phase I trial of advanced cancer patients (*56*). Retinol was found to cause dose-limiting central nervous system toxicity and hepatomegaly at a dose of approximately 300,000 $\mathrm{IU \cdot m^2 \cdot day^{-1}}$ after 4 months. Retinol was tolerated at 200,000 $\mathrm{IU \cdot m^2 \cdot day^{-1}}$ for periods up to 1 year. Case reports (*57*) of vitamin A toxicity after 6–10 years at 25,000 to 50,000 IU/day suggest that side effects can occur with prolonged use at such levels.

Our dosage of 20,000 IU/day is not intended to be the maximal well-tolerated dose. This dose level, which is available “over the counter,” has more limited aims, primarily the correction of deficiency or borderline deficiency of plasma retinol.

Subjects will receive a 4-month supply of the 13-cRA/retinol combination or placebo following randomization with a daily dose in each capsule of a monthly punch-out card of capsules. Within a 4-month cycle, we will have subjects contacted by telephone after 2 months in a standardized manner to encourage compliance and to identify any prominent side effects, whereupon a clinic visit would be requested. Subjects will return to the clinic at the end of 4 months for physical examinations, blood tests, and new supplies of capsules. Detailed toxicity monitoring (including blood samples for determination of triglycerides, cholesterol, serum glutamic-oxaloacetic transaminase, and alkaline phosphatase) will be done in conjunction with the clinic visits. Dosage modification will arise from development of any serious dermatologic, endocrinologic, metabolic, neurobehavioral, or other toxicity. An unblinded Toxicity and Endpoints Committee will review all patients requiring dosage modification.

In addition to self reports, we will monitor compliance by measuring blood concentrations of retinyl palmitate, 13-cRA, and 4-oxo-cRA. Negligible values in the treated group will indicate their failure to take the medication. However, these assays are not sensitive enough to detect a few missed doses.

The intended duration of treatment is 5 years, with an additional period of follow-up. Based on the results of Berry (*12*), a subject at age 55 with less than 50% disability at the time of asbestosis certification has a life expectancy of over 10 years. Thus a postintervention follow-up period of 5 years may be feasible.

The incidences of lung cancer and mesothelioma are the principal study end points. Cancer occurrence will be actively monitored by annual questionnaire and telephone contact and, in addition, will be monitored by computerized match with our population-based cancer registry, which is a part of the national Surveillance, Epidemiology, and End Results system.

On the basis of Berry's (*12*) results and in view of the Selikoff-Hammond studies (*7*), we estimate 20–30 lung cancer deaths per 1,000 person-years among persons certified or certifiable with asbestosis; this estimate may be compared with 6/1,000 person-years among asbestos workers who are smokers, 1/1,000 for smokers without asbestos exposure, 0.6/1,000 for nonsmoking asbestos workers, and 0.1/1,000 for nonsmokers not exposed to asbestos. If one assumes placebo subjects enrolled in this study will develop lung cancer at a rate of 10/1,000 person-years, whereas the treated group does so at a rate of 5/1,000, then a treatment effect could be detected at the 0.05 level with probability (power) 82% based on 4,000 person-years of follow-up in each group. This suggests enrollment of about 800 persons in each group with 5 years of follow-up. To enhance statistical power and to protect against attrition and other contingencies, we intend to enroll 1,250 subjects per group over an 18-month accrual period.

Cancer incidence rates will be compared with the use of relative risk (Cox) regression techniques with control for base-line exposure levels and with appropriate attention to base-line (and subsequent) blood nutrient levels and to participants' smoking and asbestos histories. Inasmuch as their biologic processes are surely different, incidences of lung cancer and of mesothelioma will be analyzed separately. Analyses will also be conducted excluding cancers occurring in the first 2 years of follow-up. Toxicity rates will be monitored and correlated with treatment and blood nutrient levels. Cancers other than bronchogenic carcinoma and mesothelioma will, of course, also be monitored.

Chemoprevention of Lung Cancer Among Long-term Heavy Cigarette Smokers

Here we present some comments on the design of a pilot study of the use of 13-cRA and retinol in lung cancer chemoprevention in long-term heavy smokers, the rationale of which was described in the previous section. Toxicity data for 13-cRA and retinol were also reviewed above.

Persons 50–65 years old with a history of 20 or more pack-years of cigarette smoking, who are either current smokers or have quit within the past 6 years, are eligible for this study. King County Medical Blue Shield, a local medical insurance carrier, has agreed to participate in this study by allowing their subscribers to serve as the population base. Currently, there are about 36,000 subscribers in the 50- to 65-year age range in the Puget Sound area.

Exclusion criteria are identical to those in the study of persons with asbestos-related lung disease as are prestudy requirements, with the exception of asbestos exposure data. Based on an initial mailing to 1,000 subscribers, it is expected that about 12% of subscribers in the proper age range will meet eligibility criteria and will be willing to participate.

Subjects eligible and willing to participate will be stratified on the basis of age (50–60 vs. >60 yr) and smoking history (20–40 vs. >40 pack-yr). Subjects will be randomized within strata, subject to the additional constraint that those within the same household (husband/wife subscribers may enroll) will be assigned to the same treatment group. There will be 4 treatment arms: placebo; 25,000 IU retinol/day; 20 mg 13-cRA/day; and 20 mg 13-cRA/day plus 25,000 IU retinol/day. Concern over the willingness of relatively healthy subjects to accept the mild side effects that are expected to accompany 13-cRA at 20 mg/day motivated the inclusion of a retinol-only arm. The ability to isolate side effects attributable to 13-cRA from any attributable to retinol and our desire to identify any additional side effects associated with their combination motivated the factorial design. Toxicity monitoring, dosage modification, and compliance monitoring will use similar procedures and criteria as were described above for the asbestos study.

We intend to enroll about 300 subjects in each of the 4 treatment groups over a 6-month period. This number will permit an increase in frequency of a serious side effect from 1% in the placebo group to 5% in a treated group to be detected at the $P = .05$ level with power in excess of 80%. Similarly, an increase in frequency from 5% in the placebo group to 10% in a treated group could be detected with nearly 80% probability. Similar comments apply to side effects in the combination compared with the single-agent arms.

The length of treatment in this pilot study is 3 years. On the basis of 4 monthly analyses of side effect rates, blood retinol and 13-cRA levels, and compliance, decisions will be made concerning a full-scale intervention trial. We hope that not only the placebo group but also a treatment group from the pilot study will continue their assigned treatment for another 3 years and will serve as a vanguard group in respect to cumulative toxicity and compliance for the full study. It is expected that the full study will require at least 15,000 enrollees made up of King County Medical Blue Shield subscribers and perhaps subscribers to other health care insurance programs.

Chemoprevention of Cervical Cancer Among Women With Mild or Moderate Dysplasia

As described in the previous section, motivations are strong for our repeating some form of intervention trial that would help examine the effect of folic acid on progression or regression of cervical dysplasia. The eligibility criteria for the Seattle-based trial include a colposcopically directed, biopsy-proved diagnosis of CIN I or CIN II. Additional eligibility criteria include total visualization of the squamocolumnar junction (with colposcope) and a normal endocervical curettage. Potential subjects are excluded on the basis of pregnancy or intended pregnancy, use of anticonvulsant or antimalarial medications, history of diethylstilbestrol exposure, or on the basis of circumstances that are likely to prevent completion of the trial. Prestudy requirements include completion of personal and dietary interview forms and blood drawing. Blood samples will be used for serum folate and red blood cell folate, β-carotene, retinol, determinations of vitamins E and B_{12} and ascorbic acid, and for viral antibody titers.

Potential subjects are identified from pathology reports at the University of Washington, Swedish, and Virginia Mason Hospitals. Consenting subjects will be stratified on the basis of degree of dysplasia (CIN I vs. CIN II) and will be randomized within strata in a double-blind fashion to receive either 5 mg oral folic acid/day or placebo for a minimum of 12 months. Twice this daily dose has been used in the intervention study previously mentioned (*46*) with no reported adverse effects. However, others (*58*) have reported mental changes, sleep disturbances, and gastrointestinal disturbances at 15 mg/day. Hellstrom (*59*) and Richens (*60*) who did subsequent well-controlled studies and who used this same dose rate did not detect any disturbance in mental status or sleep patterns associated with folic acid. However, other researchers (*61, 62*) have observed allergic reactions among patients receiving as little as 15 mg/day. In view of and the possibility that side effects may be cumulative over the period (at least 12 mo) of folic acid administration, 5 mg/day has been chosen as a prudent dose rate.

Women will be scheduled for a clinic visit every 3 months during the first year of participation. At the clinic visit, subjects will have 2 Pap smears and a colposcopy performed as well as a photograph taken of the cervix showing abnormal areas. Serum folate will be measured at the first 3-month visit so that we can monitor blood folate level and assess compliance. In the Butterworth et al. study (*46*), the rise in serum folate levels was almost eightfold among persons receiving 10 mg folic acid/day. Pill counts will also help us monitor compliance. Serum and red blood cell levels will be repeated on a subset of patients at the 6- and 9-month visits as will serum B_{12} and other nutrient levels for all patients at the 12-month visit.

Various techniques will be used in our attempts to ensure that a large fraction of women complete at least 12 months of protocol compliance. All cytologic specimens will be evaluated blindly at a centralized laboratory. Study end points will not only include the conventional cytologic measures but also measurements of macrocytosis, aneuploidy, and micronuclei. Disease progression will be defined by the presence of more severe abnormalities than originally found by cytologic smear and a more abnormal appearing cervix by colposcopy. Regression to normal epithelium will require 2 pairs of "negative" cytologic smears at consecutive visits with no visible abnormality of the cervix by colposcopy. Women who have progressed to carcinoma-in-situ or invasive cervical cancer on the basis of Pap smear and colposcopy will undergo further diagnostic procedures and, if confirmed, will be taken off study so they can receive more aggressive therapy.

Our goal is to enroll 150 subjects in each arm of this study. The participating clinics care for about 133 patients per year who meet the eligibility criteria for the trial. Assuming a 75% participation rate and a follow-up rate of 70% or greater, a sufficient number of patients can be enrolled in a 4-year period. These numbers will allow detection of a 25% difference in regression rates between the 2 groups at the $P<.05$ level with power of 80%. Patients entered into the study early will continue to be followed for progression. In view of the lower progression rates compared with regression rates, an average of about 4 years of follow-up will be required for us to detect a 50% improvement in progression rates at the 5% significance level with a probability of 70%. Time to regression and progression data will be analyzed by relative risk regression methods. Cytology scores will be compared by ordinary linear regression methods.

DISCUSSION

A number of generic issues arise in the design and conduct of cancer chemoprevention studies. For example, should a study be targeted toward the prevention of a specific cancer or to evaluation of the efficacy of a specific agent? It seems to us that priority should initially be given to designs aimed at demonstrating an ability to prevent cancer, even if extraction of the precise role of the agents involved is not possible. Following such a demonstration, we believe there will be ample motivation for isolating the most effective agents and dosages. This viewpoint argues for chemopreventive strategies involving a combination of agents, at least during this early phase of cancer chemoprevention research.

Other issues pertain to the selection of study subjects. For example, should extremely high-risk subjects be selected or is chemopreventive effect more likely in a group of persons with more moderate risk? Clearly one needs to know a good deal about disease mechanisms and agent mechanisms of action to answer such questions. Practical constraints would appear to dictate the selection of relatively high-risk persons for early studies, but we will need to remember that the efficacy of a particular agent may depend on the characteristics and exposures of the subjects. "High risk" in some contexts corresponds naturally to "late stage" for a carcinogenic process. In restricting attention wholly to high-risk individuals, one may then be limiting the chemopreventive effort to interventions that impact the late stages. Even so, such studies represent an important distinction in concept from the cancer therapeutic trial.

Another issue in the choice of subjects relates to population generalizability. In contrast to the typical therapeutic trial in cancer, one may have opportunities for identifying eligible subjects as a probability sample of a defined, perhaps geographically defined, population. Because participation rates in a chemoprevention trial may be low, collection of basic demographic and risk factor data on eligible subjects, whether or not they choose to participate, should be encouraged so that generalizability is enhanced.

Important practical issues also arise in the conduct of long-term chemoprevention trials on relatively healthy persons. For example, is it possible for one to monitor side effects effectively in the absence of a clinical context? Even if good technologies exist for thorough monitoring, can such monitoring be done with acceptable demands on the participants (e.g., for interviews and blood letting), and can such monitoring be done with acceptable cost? Certainly, the recent large-scale cardiovascular disease prevention trials have devoted an admirable degree of attention to monitoring of side effects, but the costs appear to have been staggering. Similarly, how can one most effectively maintain compliance over the extended period of drug administration that will typically be required for a chemopreventive trial? Periodic subject contacts, pill counts, and the use of suitable biochemical measures all appear to be useful devices with which we can document and enhance compliance. However, there are trade-offs: Intensive encouragement may reduce the practical implications of trial results because such encouragement will likely be unavailable in a general population application of an intervention strategy. More importantly for the trial itself, frequent subject contact may well lead to control group contamination, as control participants are periodically reminded of their high risk status and seek to identify and apply life-style changes that may reduce their risk. For example, such contamination apparently took place to an unanticipated extent in the "usual care" group in the Multiple Risk Factor Intervention Trial (*63*). On the other hand, fear of contamination is insufficient reason for laxness in the reinforcement of compliance because, for some chemopreventive agents, continuity of intake may be a prerequisite to efficacy. In some studies, a "run-in" period, in which all subjects receive a placebo, may usefully lead to the identification and exclusion before randomization of obvious noncompliers.

The ability to maintain blindness over a long-term trial is another issue. What increase in the frequency of side effects in an intervention group is consistent with blinding and the maintenance of a placebo control? Under what circumstances should blinding be foregone in favor of avoidance of contamination and cost containment?

The issues mentioned above are but a subset of design characteristics that have been considered to varying extents in the study designs described. At the time of this writing (January 1984), the studies have been funded by the Division of Cancer Prevention and Control of the National Cancer Institute, and approval of a toxicity review committee appointed by this Division also has been obtained. However, patient enrollment awaits approval of detailed protocols and formulation of the medications. The suggestions of commentators and conferees may still influence the study design and are sincerely welcomed.

NOTE ADDED IN PROOF

A number of changes were implemented in the study design described above, prior to the beginning of subject enrollment. Most notably, beta-carotene was substituted for 13-cRA in both the asbestos-related lung cancer prevention trial and in the lung cancer prevention pilot trial among long-term cigarette smokers. For those wishing to correspond on specific trials, the principal investigators are Dr. Gilbert S. Omenn (asbestos-related lung cancer), Dr. Gary E. Goodman (cigarette smoking-related lung cancer), and Dr. Joseph Chu (cervical dysplasia regression and progression).

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Chemoprevention of Oral and Esophageal Cancer in Uzbekistan, Union of Soviet Socialist Republics [1]

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ABSTRACT—The results of a survey of a population with a high risk of oral and esophageal cancer and the outline of a chemoprevention scheme for persons found to have a precancerous condition of the mouth and esophagus are presented. Of a total of 1,569 men examined, 11% had preleukoplakia and leukoplakia of the mouth, and 60% of the 1,344 men in whom esophagogastroscopy was performed had chronic esophagitis. The relative risk of oral leukoplakia was highest (11.5) among men who smoke and use nass quid. The relative risk was also elevated for persons who only use nass quid (5.6) or who only smoke cigarettes (7.8). Nass use had no effect on the risk of esophagitis. A slight elevation of risk (1.9) of esophagitis was observed for current smokers and drinkers. Of the men from whom blood was drawn for analysis, 4%, 66%, and 86% had low levels of retinol, carotene, and riboflavin, respectively. The high prevalence of oral and esophageal precancerous conditions and low blood levels of riboflavin, carotene, and vitamin A observed in the surveyed population, as well as the existing evidence on the possible protective effect of these nutrients in carcinogenesis, provide an opportunity and a justification for the chemopreventive trial, with the regression of observed precancerous lesions as the end point of the study.—Natl Cancer Inst Monogr 69: 259-262, 1985.

The incidence of oral and esophageal cancers is considerably higher in the central Asian republics than in other regions of the Soviet Union (*1-3*). This increase in risk of oral cancer in this area is attributed to residents using nass quid, which is a mixture of tobacco, ash, cotton oil, and lime (*2*). The causes of the increased incidence of esophageal cancer in this same area are still unknown, although the possible role of vitamin deficiency has been implicated (*3*). Data accumulated from other studies suggest that the risk of esophageal cancer is associated with alcohol consumption, cigarette smoking, drinking of hot beverages such as hot tea, use of opium, and vitamin deficiency (*4*). Results of studies in northern Iran have shown that the risk of esophageal cancer is increased in persons consuming a diet low in fruits and vegetables (*5*). Diets deficient in riboflavin and vitamin A have been observed in an area with a high risk of esophageal cancer in northern China (*6*).

The risk of oral (*7*) and esophageal (*8-11*) cancer has been associated with precancerous lesions, i.e., morphologically altered tissues in which cancer is more likely to occur than in apparently normal counterparts (*12*). In the mouth, 2 types of clinically recognizable precancerous lesions may occur: leukoplakia (including preleukoplakia) and erythroplakia (*7*). The prevalence of precancerous lesions of the oral mucosa (leukoplakia) varies, according to different surveys, from 0.2 to 11.6% (*7*). The prevalence of leukoplakia in one of the surveys conducted in Uzbekistan was found to be 5.5% in persons presently addicted to nass versus 0.1% among persons who did not chew nass and nonsmokers (*2*). Leukoplakia usually occurred in sites within the oral cavity that came into contact with the tobacco-containing mixture. The frequency of oral lesions is increased in those with simultaneous addiction to nass and cigarette smoking (*2*).

The test for the frequency of the formation of micronuclei that seems to reflect chromatid and chromosome aberrations occurring in the proliferating basal layers of the mucosa has been applied to persons at high risk of oral cancer. The frequency of micronuclei formation is elevated in persons who chew betel nut or other types of quid compared with those who do not (*13*). The micronuclei, which are detectable in exfoliated mucosal cells, are formed from chromosome fragments and aberrant chromosomes not included during their mitotic cycle in the main nucleus (*14*).

Some (*8-11*) have suggested that chronic esophagitis is a precursor of esophageal cancer. Kolicheva (*8*) and Kolicheva et al. (*9*) described the high prevalence (66 and 88%) of chronic esophagitis in 2 areas with a high incidence of esophageal cancer in Kazakhstan in a series of autopsies on people who had died from causes other than esophageal cancer. The same authors (*9*) reported 70 cases of esophagitis that were diagnosed endoscopically.

Chronic esophagitis was discovered in 66% and 85% of the population in North China and North Iran, respectively, during the population-based endoscopic survey in areas with a high incidence of esophageal cancer (*10, 11*).

MATERIALS AND METHODS

All 2,150 males in the 55- to 69-year age group, residents in one local authority district (Narpai region, Samarkand Oblast of Uzbek Soviet Socialist Republic), were invited to attend a medical examination by local nurses, who personally delivered to them a special invitation letter. Of those invited, 1,504 came for the screening. In addition, 65 men who were under 55 or over 70 years old came for a check-up without being invited. For all 1,569 men, questionnaires were completed containing information on demographic characteristics, use of nass, cigarette smoking, alcohol consumption, medical history, family history of cancer, and symptomatology. The interview was followed by an oral examination and esophagogastroscopy. All had oral examinations, whereas esophagogastroscopies were performed on only 1,344. When any oral or esophageal lesions were discovered, photographs were always taken; samples for cytologic and histologic investigation were also obtained. In addition, oral and esophageal smears were taken for the detection of micronucleated cells. Blood was collected from a 20% sample of persons examined for analysis of the levels of retinol, beta-carotene, and riboflavin.

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[5] We thank Mrs. R. Zaridze and Mrs. S. Dartoy for their assistance with the data retrieval.

Endoscopic examination was performed with a fiberoptic, forward-viewing esophagogastroscope. The biopsy specimens were fixed in 10% formalin and stained with hematoxylin and eosin. Mucosal scrapings were taken from the oral mucosa for cytologic examination. Cytologic specimens of esophageal mucosa were also prepared for examination. Histologic and cytologic reviews of the oral and esophageal specimens were done at the All Union Cancer Research Centre of the Academy of Medical Sciences in Moscow. The test for the frequency of micronucleated cell formation was performed at the Environmental Carcinogenesis Unit of the British Columbia Cancer Research Centre in Vancouver, Canada. Biochemical analyses of blood for vitamin A, beta-carotene, and riboflavin were performed by Dr. David Thurnham at the Clinical Investigation Unit of Dudley Road Hospital (Birmingham, United Kingdom).

In an initial attempt to analyze the relationship between the use of nass, cigarettes, and alcohol on the risk of oral leukoplakia and chronic esophagitis, we fitted hierarchies of models using the generalized linear interactive modelling (release 3) system (*15*).

RESULTS

Of the total of 1,569 men interviewed, 91% were ethnic Uzbeks, 3% ethnic Russians, and 6% other Orientals; also, 75% were agricultural workers and 25% were residents of 2 small towns; 636 men (41%) reported nass quid chewing; 259 (17%) were cigarette smokers; and 736 (47%) stated that they drink alcoholic beverages.

Medical histories of upper gastrointestinal tract diseases were reported by 282 men (18%), and 499 men (32%) told of having related symptoms. Family history of upper gastrointestinal tract cancer was reported by 143 (9%).

Angular stomatitis, a disorder suggested as being a symptom of riboflavin deficiency, was observed in 332 (21%) of the men examined.

Precancerous oral lesions such as preleukoplakia and leukoplakia were diagnosed in 43 (3%) and 127 (8%) persons, respectively. In all, 191 lesions were diagnosed: 144 (75%) of leukoplakia and 47 (25%) of preleukoplakia. The most frequent sites for these lesions were the lower labial mucosa (7%), labial commissure (10%), buccal mucosa (32%), followed by the lower surface of the tongue and the tip of the tongue (38%).

Three patients had cancer of the mouth; in 2, the primary site was the floor of the mouth, and in the other, it was in the lower alveolar ridge.

A diagnosis of chronic esophagitis, based on both endoscopic and histologic examinations, was made in 807 (60%) of the men examined. Chronic esophagitis was catarrhal in 89% and erosive in 11% of the patients, of whom 22% were classified as having mild cases, 32% as severe, and 47% as moderate. Dysplasia was diagnosed in 4.1% of the men with esophagitis.

The most frequent site for esophagitis was the middle third of the esophagus (28%), followed by the lower third (22%). Of the patients with erosive esophagitis, the lesions of 11% were located in the middle and lower thirds of the esophagus, and 79% were in the lower third. In 361 (45%), esophagitis was accompanied by incompetence of the cardiac sphincter, a condition that was associated with hiatal hernia in 111 patients. Different types of oral leukoplakia or preleukoplakia were observed in 120 men with chronic esophagitis.

Squamous cell carcinoma of the esophagus was diagnosed in 8 patients. In 6, the primary site of cancer was the middle third of the esophagus and in 2 the lower third. Adenocarcinoma of the stomach was diagnosed in 7 subjects.

The prevalence of oral leukoplakia, preleukoplakia, and esophagitis in relation to different habits, such as nass chewing, cigarette smoking, and alcohol consumption, was investigated. The best fitting model found to explain the data was one involving the main effects of nass and smoking plus an interaction term. A term for alcohol use was not necessary because this factor did not appear to exert any influence on the probability of oral leukoplakia when we allowed for the effects of nass and smoking. The relative risks obtained under this model are presented in table 1. Risks in present nass users who are nonsmokers (5.6) and present smokers who do not use nass (7.7) are essentially similar; so too is the risk in those who previously used nass and smoked (7.1). The risk is especially elevated among those who presently smoke and use nass (11.5).

The best fitting model obtained for esophagitis included the main effects for smoking and alcohol consumption and an interaction term. There appeared to be no effect

TABLE 1.—*Calculated relative risks of oral leukoplakia according to smoking and nass use based on a statistical model*[a]

Nass user	Cigarette smoker					
	Nonsmoker		Former		Present	
	RR	CI	RR	CI	RR	CI
None	1.0	—	1.8	0.5– 6.3	7.8	4.4–14.2
Former	1.4	0.2–10.7	6.6	1.7–25.7	—	—[b]
Present	5.6	3.4– 9.5	2.5	0.7– 8.8	11.5	5.4–24.3

[a] RR = relative risk; CI = 95% confidence interval.

[b] Calculated risks are unreliable because of the small numbers of patients in these cells.

for nass use. The association, as measured by the overall improvement in the fit of the model, did not appear to be as strong between these factors and esophagitis as the previous association between smoking, nass, and leukoplakia, although the risk among current smokers and drinkers was equal to 1.9, with 95% confidence interval of 1.0–3.5.

Examination of cytologic samples for the frequency of micronucleated cells has shown the elevated frequency of these cells in the oral mucosa of men who chew nass to range from 1.6 to 5.8%, and in the esophageal mucosa of persons with chronic esophagitis who were nass chewers to range from 2.3 to 5.2%. The controls (nonsmokers and nonchewers) have a frequency of micronucleated cell formation ranging from 0.0 to 0.8%. Persons who used nass had an elevated frequency of micronuclei formation, independent of the presence of oral leukoplakia.

Riboflavin status measured in 322 men on the basis of the erythrocyte glutathione reductase activation coefficient was normal (i.e., they had an activation coefficient below 1.30) in only 14% of the subjects, whereas 9% and 77% had an activation coefficient greater than 1.80 and 1.30, respectively.

Plasma retinol and carotene concentrations have been measured in 150 men. Plasma retinol concentrations were low (<20 μg/dl) in only 4% of the men, and 1 man had a value of less than 10 μg/dl, which is indicative of a retinol deficiency. However, the distribution tended to be skewed toward lower values. In 66% of the subjects, plasma carotene concentrations showed low values (<40 μg/dl), and 25% had values less than 20 μg/dl, also indicative of a deficiency.

DISCUSSION

We have presented the results of the survey of a population with high risk of oral and esophageal cancers. This population appears to have several interesting epidemiologic characteristics, most probably associated with the high risks of oral and esophageal cancers.

First of all, 11 and 60% of the men examined have oral leukoplakia and chronic esophagitis, conditions suggested to be precursors of cancers of the mouth (*2, 7, 16*) and esophagus (*8–11*).

Secondly, a remarkably high proportion (41%) of the men surveyed were nass chewers, and this habit, like the chewing of other types of quid, has been related to oral cancer (*2, 7, 16–18*). A relatively low proportion of the men surveyed smoked cigarettes (17%).

Thirdly, 4, 66, and 86% of the men who provided blood for determinations had low values for retinol, carotene, and riboflavin, respectively, vitamins that most probably have a protective effect against the development of cancer (*19–24*). These results corroborate those of the study by Thurnham et al. (*6*) in China, i.e., a ribloflavin deficiency was revealed in both areas. However, the vitamin A deficiency reported in 42% of the Chinese subjects was present in only 4% of our study population, whereas the lack of sufficient carotene we observed in 66% of our men was reported in only 6% of the Chinese tested.

Analysis of the relationship between nass chewing and cigarette smoking and oral leukoplakia and esophagitis revealed that the risk of oral leukoplakia is highest among those who presently chew nass and smoke (11.5) and is such as to indicate a simple additive increase in risk by the presence of these 2 factors. The risk was also elevated among those who only chew nass (5.6) and who only smoke cigarettes (7.8). These elevated risks suggest that they could be halved by the elimination of one or the other of these habits.

Nass use appears to have no effect on the risk of esophagitis. A slight elevation of risk (1.9) was observed for current smokers and drinkers. However, some other factor that was not included in the statistical analysis may be responsible for the risk of esophagitis.

In recent years, the role of vitamins in the etiology and prevention of cancer has attracted considerable interest. Studies on laboratory animals indicate that vitamin A deficiency increases susceptibility to chemically induced neoplasia and that an increased intake of this vitamin appears to protect against carcinogenesis (*20*). Carotenoids are precursors of vitamin A and are converted into vitamin A in vivo. Carotenoids can also be absorbed from the gastrointestinal tract. Peto et al. (*19*) suggested that beta-carotene itself may have the capacity to inhibit carcinogenesis.

Epidemiologic studies have shown that increased intake of vitamin A and beta-carotene in the form of foods with a high content of these vitamins decreases the risk of cancer of the mouth, esophagus, and lung (*25*). However, these data do not show whether the effect is due to vitamin A itself or carotenoids.

The evidence from animal experiments indicates that riboflavin deficiency increases the yield of chemically induced tumors of the skin and esophagus (*22, 24*). Human studies which have indicated a possible association between the risk of esophageal cancer and riboflavin deficiency are consistent with our findings (*5, 6, 10, 11*). The Plummer-Vinson syndrome, which is known to increase the risk of esophageal cancer, is associated with riboflavin deficiency (*23*).

The mechanisms of action of the discussed putative protective factors differ and, most probably, they act at different stages of carcinogenesis. For example, the mechanism of the protective effect of vitamin A against cancer is most likely associated with its involvement in the cell differentiation and proliferation process (*19, 20*), whereas beta-carotene is a free radical trap and one of nature's most important defenses against singlet oxygen (*19*). It has been suggested that riboflavin deficiency might facilitate the neoplastic process by impairing cellular respiration (*22, 23*). For these reasons, combinations of different inhibitors of carcinogenesis, acting at multiple points, are likely to be more effective than any single inhibitor alone.

In an intervention trial on a healthy population, the use of protective factors inhibiting the formation of carcinogens would be more relevant (e.g., in industrial situations in which prevention entails reduced exposure to exogenous carcinogens). In the chemoprevention trials on persons with precancerous lesions, i.e., disease processes in which failure of the cell differentiation mechanism plays a prominent role in addition to administering factors blocking carcinogen formation, substances believed to normalize the cell differentiation process would be required.

CHEMOPREVENTION TRIAL

The high prevalence of oral leukoplakia and chronic esophagitis conditions suggested to be precancerous and the observed deficiencies for riboflavin, carotene, and vitamin A in the surveyed population, as well as the existing evidence on the possible protective effect of the aforegoing substances in carcinogenesis, provide both an opportunity and a justification for a chemopreventive trial, with the *regression* of observed precancerous lesions as the end point of the study.

The intervention trial which is now in progress involves random allocation of all eligible subjects with oral leukoplakia and esophagitis (780 in all) to 1 of 4 arms in a double blind 2×2 factorial design, with the active arms defined by the administration of riboflavin and a combination of retinol plus beta-carotene. Weekly doses of vitamin supplements are 100,000 IU for vitamin A, 280 mg for beta-carotene, and 200 mg for riboflavin.

Six months and 1 year after initiation of treatment, oral examinations will be performed and scrapings will be taken from the oral mucosa for the micronucleus test. The effect of treatment on the frequency of the formation of micronuclei should, in principle, become detectable in a much shorter time span than any effect that might be detected by routine cytology and histology. The persons in the trial will be under constant and close surveillance by local doctors and nurses, and this should ensure a high compliance rate.

The results of the intervention will be assessed according to the following parameters: 1) oral examination before, during, and after treatment; 2) endoscopic investigation before and after treatment; 3) histologic diagnosis before and after treatment; 4) test for the frequency with which micronuclei are formed in the oral mucosa before, during, and after treatment; 5) test for the frequency of micronucleus formation in the esophageal mucosa before and after treatment; 6) analysis of blood levels for vitamin A, beta-carotene, and riboflavin before, during, and after treatment.

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Discussion of Chemoprevention Trials [1]

Brian MacMahon [2]

Dr. Henderson's asking me to comment on the intervention studies that have been described to us today is analogous to asking the second fiddle of the Prairie Home Companion Band to comment on a rendition of a Mahler Symphony by the Chicago Symphony Orchestra. Intervention studies in humans aimed at prevention are expensive and enormously consuming of scientific resources and the public's patience. They therefore do not receive governmental support without considerable thought and careful consideration by the most knowledgeable investigators available, as evidently has been true with the studies about which we have heard. However, if the second fiddle referred to were asked to give an opinion, no doubt he or she would not hesitate to do so, probably regardless of whether he or she had heard the particular rendition, inasmuch as everyone is entitled to an opinion.

I offer these comments in that spirit, as those of the opinion of a man-in-the-street, not the scientific critique of an expert. All the issues I will raise have been considered by the investigators involved and resolved in favor of the proposals presented. I am quite sure that the investigators themselves were not unanimous in the selection of resolutions for the various issues, and, in many instances, the choice must have been that of the least undesirable among options that all seemed undesirable to some degree.

The issues on which I would like to comment fall into three areas: 1) Should we do randomized studies of cancer prevention at this time? 2) Are these studies testing the best hypotheses? 3) Are the studies being properly conducted?

Should we do randomized studies of cancer prevention at this time? As we all know, there are stages in the development of knowledge when randomized studies are appropriate and others when they are not. At one extreme, we may know too much to suggest randomization, e.g., to randomize a smoking cessation program among persons with asbestosis, or even in a general population, would be unethical. At the other extreme, we may know too little. Observational evidence of the existence of a relationship may not be sufficient to justify the commitment of resources to a randomized trial of a substance which may prove not only ineffective but potentially harmful. The width of the band between these extremes varies among individuals and among disciplines. It is, I suppose, broadest among statisticians. Fear of retribution prevents me from naming the disciplines in which the band seems to be narrowest or even nonexistent.

My own band is fairly broad and I do believe that randomized prevention trials in cancer or, for that matter, almost any other disease I can think of are warranted at this time. I say this despite the relative flimsiness of the evidence that supports the hypotheses underlying these particular trials, and despite my prediction that none of the trials presented today will demonstrate a preventive effect of the regimen being tested. The volume of human experience that passes without making any contribution to the knowledge available to future generations is appalling, often simply because it is not recorded, much less randomized. I have been taking daily for 20 years 2 medications in the belief that they may increase the number or quality of my later years. I have no great faith that they will accomplish either of these objectives, but the medications are cheap, and, I am told, without side effects. However, I am bothered that, whether I end up in a renal dialysis unit or live to the age of Methuselah, my fate will contribute absolutely nothing to man's knowledge of the effects, good or bad, of these 2 medications. I am of the generation, educated by Bradford Hill, that is willing to randomize at the drop of a hat. Indeed, as Hill once reported, not knowing whether to write these comments down or speak spontaneously, I thought I should, like him, decide through the proper process of reference to a book of random numbers. I had to open it five times before I got the right answer.

Given that frame of reference or state of mind, do I think these studies are asking the right questions? Without even thinking about it, one must answer yes to this question. The hypotheses have been selected by the persons most familiar with each problem in consultation with a broad group of investigators. These hypotheses must be worth investigating. Neither I nor anyone else is in a position to choose better hypotheses, even though one may express a personal opinion that none of them will be confirmed. One hopes that this is not the case, but, even if we are disappointed with the results of some or all of these trials, at least some of the brush will have been cleared away, and we will be better able to look for the villains or angels in other places. The least we can expect from these trials is the accumulation of a lot of epidemiologic information about the diseases they address and useful experience in the logistics of conducting single and collaborative trials in various parts of the world.

This is not to say that these are the *only* trials that would be appropriate. On the basis of what we heard during these sessions, I would think that a stronger case than has been made for any of these trials could be made for a trial of the elimination of salt fish in the diets of Chinese infants and children. The units of randomization would have to be populations, rather than individuals, or some acceptable substitute would have to be found and provided, and a 30- to 40-year study period required. However, in my assessment of the current evidence, the probability of a successful outcome is extremely high. This is one example of a situation in which a public health action, if properly designed, can also serve scientific purposes.

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[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

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I have a personal prejudice in favor of single-factor trials. I was never in favor of the Multiple Risk Factor Intervention Trial for cardiovascular disease. If it had been successful, those of us who wish to do only those things that we are sure are good for us would still not have known whether giving up smoking alone was sufficient to derive the benefit. Because the trial was not successful, or debatably so, we do not have to worry. On the other hand, the success of the single-factor trials of hypertension and, more recently, of blood lipid reduction, give the clear message that giving up smoking is not enough.

For this reason, I prefer the Seattle over the China trials. Although 2 of the Seattle trials include 2 agents, they belong to the same class of compounds and in 1 of them a factorial design will permit evaluation of each of the 2 agents separately. On the other hand, in the Chinese trial aimed at esophageal cancer, the decision has been made to have only 2 arms, one of placebo and another which includes multiple agents, not even from the same class. This decision has been made after careful consideration of all the alternatives and must be respected. I state only that my inclinations would have gone against such an approach. If the trial is successful, I am afraid that we will be in the same position as after a successful Multiple Risk Factor Intervention Trial. I suppose that, in favor of this multiple treatment, one could say that if the trial were unsuccessful, i.e., demonstrates no differences between treatments, we will have eliminated a greater number of hypotheses than if we had had single agents in each arm. However, not many trials are rationalized on the hope that they will be unsuccessful. Nevertheless, I acknowledge the public health considerations that entered into the investigators' final decision.

Lastly, with respect to the conduct of these studies, I am sure that the expertise available to these investigators will ensure the most careful consideration of the logistics of conducting the trials. I have only two comments.

It seems to me, at least as I understand from the planning documents sent to me by Dr. Blot, that the goals of the pilot study for the Chinese esophagus study are broader than would usually be the case and in some ways are questionable. For example, it is said that final decisions on the vitamins and minerals to be included will be made *after* the pilot study. A pilot study is used to test feasibility, the logistics of delivery of the agent, acceptability, compliance, etc., as indeed is also planned in this study. It is not clear to me how the results of the pilot study can help us decide which agents are to be tested; surely, these decisions depend on rationales based on evidence external to the study itself.

Also, I would like to comment on the folic acid–cervix cancer study. This one stands or falls on the validity of the cervical cytology readings. As far as I could tell from the document Dr. Prentice supplied me, the cytologic readings that determine eligibility for the study as well as the outcome variables are those of the individual clinics, and no provision has been made for central reading of slides and biopsy specimens. Even if there were provision for central reading, though I would feel better, I would not be entirely reassured. Although we recognize that reproducibility of cytology readings is lacking, I believe that we do not realize just how bad the situation is. I would feel more confident if provision had been made to incorporate, at a minimum on a sample basis, the new techniques for quantification of DNA and estimation of polyploidy, a characteristic highly related to future neoplasms.

In summary, I am pleased that investigators are willing to devote their skills to these studies and that the necessary financial resources are being made available to them. However, I judge that the benefit derived from these trials will not come principally from the testing of the hypotheses that stimulated them.

Concluding Remarks [1]

Joseph F. Fraumeni, Jr. [2]

As a participant in the first Symposium of this series held in 1975 and now the fourth nearly a decade later, I find it interesting to consider some trends and developments that have occurred in the intervening period.

The Pacific Basin is obviously far better represented at this meeting than at the first, with at least twice the number of participants coming from many more areas. Especially interesting is the much higher percentage of female participants here, apparently reflecting the recent welcome influx of women into the field of epidemiology. The group also seems much younger now, although this might represent a form of ascertainment or recall bias on my part. Still it is good for us to continue to see those pioneers who have contributed so much knowledge about cancer epidemiology in the Pacific Basin, such as Mr. William Haenszel, who conducted the excellent studies of migrant populations, and Dr. Takeshi Hirayama, who has conducted and stimulated field investigations in many areas of the Pacific.

A major development since the first meeting has been the establishment of contacts and exchanges with Chinese epidemiologists, leading to their major participation in this meeting and to exciting new collaborative studies involving Chinese and American investigators. It is striking to see the many epidemiologic opportunities afforded by the large and accessible populations in China, the remarkable geographic variation in mortality rates detected by the cancer atlas of China, and the changing cancer risks of Chinese migrant populations in various parts of the world.

The first meeting in 1975 focused on descriptive epidemiology and the identification of gaps in our knowledge of the patterns of cancer in the Pacific Basin. Since then, many of the gaps have been filled. Emphasis has also shifted from hypothesis-generating descriptive studies to analytical case–control and cohort strategies aimed at testing etiologic hypotheses. However, it is clear from this meeting that descriptive epidemiology, including the monitoring of time trends, continues to contribute important new etiologic clues and serves also as a guidepost in our evaluating the plausibility of suspected risk factors.

Although demographic patterns are useful in developing new leads to etiology, the presence of Dr. John Ho at this conference has reminded us of the critical role played by the alert practitioner over the years. Dr. Ho's original clinical observations on nasopharyngeal cancer in Hong Kong have provided a major impetus to etiologic research, and his experimental work on this tumor has also helped to spark further investigation.

Since the first Symposium, we have witnessed a rapid accumulation of etiologic leads and an expansion of epidemiologic activity aimed at clarifying a wide variety of risk factors, including tobacco products, alcohol, radiation, certain occupational exposures and environmental pollutants, microbial agents, genetic susceptibility, and, particularly in recent times, diet and nutrition. However, the more we learn about dietary habits and cancer risk, the more complex and confusing the relationships seem. At times the situation may become frustrating, as during this meeting, when conflicting results were presented about particular associations. However, the state of affairs is really far better than that prevailing at the first Symposium. At that time, epidemiology was just starting to move toward the mainstream of cancer research, and there seemed to be a paucity of new ideas about the causes of many common tumors and a vague sense of discomfort in the ability of our relatively small band of cancer epidemiologists to meet the challenges ahead.

The epidemiologic studies presented at this Symposium indicate the progress that has been made toward a better understanding of the distribution and origins of cancer. The contributions of epidemiology have helped not only in detection of carcinogenic hazards but also to some extent in clarification of the mechanisms of action, precursor states, multistage processes of carcinogenesis, and interactions between environmental and host factors. We now have a greater sense of confidence that many of the remaining obstacles to research in cancer etiology and prevention can be circumvented by epidemiologic approaches, especially when integrated with laboratory assays and new experimental probes that can lend greater precision to the identification of risks and mechanisms of carcinogenesis.

Epidemiology thrives on open communication, the sharing of new information and resources, and scientific collaboration. This series of symposia has brought together different groups of investigators willing to exchange ideas and help one another in various ways. This cooperation has extended to the development of joint ventures designed to bolster epidemiologic data resources and help ensure their full utilization. We owe our thanks to the organizers of this Symposium, which, like the earlier meetings, has succeeded in its mission of stimulating new collaborative inquiries and enhancing the potential of epidemiologic research to elucidate the causes and means of preventing cancer.

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[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

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WORKING GROUP SUMMARIES

Diet and Cancer	Anthony J. McMichael
Hormones	Noel S. Weiss
Other Life-style Factors	Robert MacLennan
Cancer Registration	Donald F. Austin

Working Group Summaries [1, 2]

DIET AND CANCER

As has been evident from the presentations during this Symposium, the etiologic relationship of diet to cancer is an uncertain and complex one, with many consequent frustrations for epidemiologists. Three broad diet-and-cancer themes have emerged here: etiologic studies of single, specific, dietary factors in cancer that predominate in non-Western populations; etiologic studies of various foods and major nutrients, singly and in combination, in cancers prominent in Western populations; and dietary intervention trials, with the use of varied intakes and combinations of micronutrients (e.g., retinols, beta-carotene, and riboflavin), seeking experimental reduction of cancer incidence or precursor progression. Aspects of the first two of these three themes were discussed in the Workshop.

Primary Hepatocellular Carcinoma

A review of the epidemiology of PHC by Dr. Mimi Yu shows that this cancer, prominent in Asia and Africa, is strongly correlated, internationally, with the prevalence of carriers of HBV infection. Prospective and case–control studies indicate that an HBV-associated RR of this cancer is between 10 and 200. Overall, HBV infection appears to be the dominant contributor to the etiology of PHC.

However, considerable ecologic human data and animal research indicates that the food mold, aflatoxin B_1, may contribute to the development of PHC. Nevertheless, the evidence from analytic epidemiology remains slight and inconsistent in 2 reported case–control studies; the 1 conducted in Hong Kong was negative, whereas the 1 in the Philippines was positive. (Data subsequently presented to the Symposium from 2 studies in China showed some ecologic association of PHC with aflatoxin B_1, but no association was observed at the household or individual level.)

A 20-year follow-up study in Kyushu, Japan, reported by Dr. T. Hirohata, has shown a positive relationship of PHC to individual consumption of strong alcoholic drinks. Furthermore, a clear dose–response relationship was present. (Data from 1 of the above-mentioned studies in China, although only preliminary, indicate a synergistic relationship between HBV positivity and alcohol consumption.)

The consistent sex difference in PHC incidence rates was pointed out by Dr. J. Ho, who noted that not only do male rates consistently exceed those for females, but that the rates begin to rise around the ages of 20–25 years in males versus 40–45 in females. Suggested explanations included differences in exposure to dietary factors (unlikely for AFB, likely but of dubious relative importance for alcohol), intrinsic sex differences in DNA repair capacity (as evidenced by animal data), the high prevalence of HBV "carriers" in males compared with females, and evidence that androgen therapy was associated with an increased risk of subsequent PHC.

The rationale for mass childhood HBV vaccination programs in high-risk populations was discussed, in view of the evidence for its predominant role in PHC etiology. Furthermore, follow-up of the vaccinated (and unvaccinated comparison) population, with observation of exposure to AFB and alcohol, would enable estimation of interactive effects between HBV and those 2 factors in the eventual data analyses.

Assessment of Total Diet and Its Role in Cancer Etiology

Dr. M. C. King presented recent findings from a case–control study in California of breast cancer in American Chinese women. In 61 patients and 61 controls, the degree of westernization of the diet and the measurement of various other specific risk factors were assessed. The index of westernization, derived in a preliminary study from a discriminant function analysis of dietary practices in U.S. Chinese and Caucasian women, showed a significant, positive relationship with breast cancer risk, as did, additionally, the consumption of poultry (vs. beef or pork) after allowance for control of a number of other measured risk factors.

This study indicated the potential importance of one's considering the whole dietary profile in relation to certain cancers, inasmuch as dietary influences on carcinogenesis may be indirect and by disturbances of hormonal and other metabolic phenomena. Different dietary components or combinations may achieve similar metabolic responses.

Dr. J. Hankin reviewed methods of assessment of diet in epidemiologic research, stressing the qualitatively different techniques appropriate to descriptive (ecologic) studies compared with analytic studies requiring assessment of the individual diet. In particular, the problems in case–control studies of assessment of usual past diet was stressed, and a set of criteria for the choice of method was

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ABBREVIATIONS: PHC = primary hepatocellular carcinoma; HBV = hepatitis B virus; RR = relative risk(s).

[1] Presented at the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16–20, 1984.

[2] These summaries are synopses of four working-group meetings held during two sessions of the Symposium; participants were invited to discuss major research issues on cancer epidemiology and cancer registration.

offered, including consideration of the validity (to be clearly distinguished from the eminently more measurable characteristic, reliability or reproducibility). True validation of retrospective diet assessment remains elusive.

Dr. Hankin suggested some areas requiring methodologic research, including comparability of diet assessment techniques, the use and relevance of biochemical markers of nutrient intake, the need for a more coherent interdisciplinary approach, and the development of new survey techniques. The particular problems of diet assessment in the multiethnic population setting were emphasized, including adaptation of the instrument to take account of culture-specific food habits, production of equivalent questionnaires in several languages, use of multilingual interviewers, and availability of satisfactory cross-cultural food composition tables.

In discussion, participants made several additional suggestions for methodologic research or at least consideration: comparison of interviewer versus self-administered diet questionnaires, the measurement of combinations of foods (i.e., meal composition), the use of sentinel food items as indices of specific nutrients (e.g., carrots for vitamin A), and the greater relevance for some cancers of measuring nutrient uptake rather than ingestion. In relation to this final suggestion, recent developments in high-performance liquid chromatography were described by Dr. C-S. Yang in relation to the enhanced opportunities for measuring a range of specific, often closely related, nutrients in blood and other body fluids.

Finally, Dr. R. K. Peters presented unpublished data from a case–control study of colon cancer in males aged less than 45 years, based on 92 case–control pairs in Los Angeles. Both occupational sedentariness (estimated from a preexisting governmental classification of activity levels in all major occupations) and several aspects of diet were associated with an increased risk of colon cancer. Emphasis was placed on the pattern of risk variation in relation to combined exposures to different diet–occupational activity configurations. In particular, it appeared that diet-related increases in risk were maximal in those in the least active occupations. This finding underscores the importance of one's stratifying on, or otherwise taking into account, relevant nondiet host factors (including sex and age) when examining cancer risk in relation to diet. This point was made on several other occasions during the Symposium.

HORMONES

This Workshop dealt with endogenous and exogenous hormones and their possible relationship to the development of cancers of the breast, cervix, and prostate.

Endogenous Estrogens and the Incidence of Female Breast Cancer

Evidence implicating endogenous estrogens in the development of breast cancer includes the reduction in risk of breast cancer associated with oophorectomy, particularly if the operation is conducted relatively early in reproductive life; increased risk of breast cancer associated with early menarche and with late age at menopause; causal role of estrogens in the development of breast cancer in a number of experimental animals; and probable differences in the excretion of estrogens (total) between premenopausal breast cancer patients and controls.

Several possible directions for future research were suggested: 1) Additional case–control studies of premenopausal breast cancer in relation to endogenous estrogens are needed that will require urine or blood samples, or both, for measurement of free and bound estrogens. Samples should be obtained at fixed times during the follicular and luteal phases of the menstrual cycle. Women without active breast cancer and women who are receiving any medication on a regular basis (e.g., women receiving chemotherapy) should be excluded from such studies. 2) Levels of urine or blood estrogens, or both, in healthy women in high- and low-risk populations, e.g., women of the same ethnic group residing in areas of high and low incidence, or women of different ethnic groups of different incidence of breast cancer residing in the same geographic area, should be compared. 3) Studies of the determinants of premenopausal estrogen levels (e.g., dietary factors) need to be conducted.

Endogenous Testosterone in Relation to the Incidence of Prostate Cancer

Evidence implicating testosterone in the incidence of prostate cancer included the following observations: Growth and function of the prostate gland is under hormonal control, e.g., the prostate atrophies following castration; in an animal model, the administration of testosterone is associated with an increased incidence of prostate cancer; some (but not all) case–control studies of prostate cancer showed increased levels of testosterone among patients; and black men living in America have a higher incidence of prostate cancer than do black men living in Nigeria, and they also have higher serum testosterone levels.

Several areas for subsequent investigation were suggested: 1) The need for additional comparisons of cases and controls for levels of serum testosterone is apparent (3 of these studies are already under way). 2) Additional comparisons of serum testosterone levels of healthy men from high- and low-risk populations, e.g., men of the same ethnic group residing in areas of high and low incidence, and men of different ethnic groups at different risk of prostate cancer residing in the same geographic area, are required. 3) Studies of factors that influence levels of serum testosterone (e.g., dietary factors) should be conducted.

Oral Contraceptive Use in Relation to the Incidence of Cervical Carcinoma

Among the evidence implicating oral contraceptive use in the development of cervical carcinoma are 5 recent case–control studies and 1 cohort study in which a relationship has been found of approximately the same magnitude (RR = 1.5–2.5). Of all the studies conducted concerning this relationship, these are the most free of the many possible biases that can affect such an association.

Suggestions for subsequent research included the following: 1) Investigators should do additional analyses of large case–control studies of invasive cervical cancer that have been and are being conducted, including examination of the role of age at which oral contraceptive use was first begun and the specific preparation used. 2) They should study the association between oral contraceptive use and the incidence of adenocarcinoma of the cervix. 3) They should also examine oral contraceptive use in relation to the individual components of the pathway leading to cervical cancer, including replication of the study that evaluated the influence of oral contraceptives on the rate of progression of dysplasia to carcinoma-in-situ, and, they should investigate the possible association of oral contraceptive use with precursors of cervical cancer.

Oral Contraceptive Use in Relation to the Incidence of Female Breast Cancer

Several case–control studies have revealed that use of oral contraceptives early in reproductive life is associated with an increased risk of breast cancer, and another study indicated that use of oral contraceptives relatively high in progestogen content early in reproductive life is also associated with an increased risk.

Early ovulation (which is associated with relatively high progesterone levels) is also associated with an increased risk of breast cancer.

Investigators of similar studies have found that use of oral contraceptives in the perimenopause is associated with an increased risk. Such use occurs at a time in which progesterone levels tend to be low.

Directions for subsequent research were suggested: 1) Existing and new case–control studies of breast cancer and oral contraceptive use are needed for evaluation of the effects of high progestogen-containing preparations taken early in reproductive life. 2) Case–control studies of women in cohorts who have commonly used oral contraceptives early in reproductive life (e.g., <20 yr of age) are recommended. 3) Perimenopausal oral contraceptive use in relationship to breast cancer, including analysis of existing data sets according to progestogen content of the birth control pills used need evaluation by case–control methods, and new studies of this type, especially in populations in which perimenopausal oral contraceptive use is common, should be initiated. 4) Research on the incidence of breast cancer in relation to use of progestogens (as supplements to noncontraceptive estrogens) during menopause would provide valuable data. 5) The potency of the various progestational agents with regard to breast tissue needs to be evaluated. (The present potency scoring schemes are based on the effect of the progestogens on the endometrium.)

OTHER LIFE-STYLE FACTORS

This Workshop was concerned with life-style factors, other than diet and hormones, which present important possibilities for epidemiologic research in Pacific Basin countries. Otherwise, no central theme was followed as in the other Workshops.

Non-phenacetin Analgesics and Renal Pelvis Cancer

Addiction to analgesics is common in certain female subcultures in the U.S., Australia, New Zealand, and Sweden. High phenacetin intake produces renal papillary necrosis which may be followed after several years by carcinoma of the renal pelvis.

Case–control studies have shown a high risk of renal pelvis cancer in heavy users of phenacetin-containing analgesics, which often contain aspirin and caffeine. Because of its toxicity, phenacetin was banned in 1970 in Australia and later voluntarily withdrawn in the U.S. Concern has been raised because it has been replaced by paracetamol (acetaminophen), the main metabolite of phenacetin. Recent case–control studies of renal pelvis cancer have suggested that non-phenacetin analgesics may produce an increased risk. However, these studies were not specifically designed for assessment of the risk of non-phenacetin analgesics.

Dr. W. Blot described a case–control study of renal cancer in Minneapolis. The strongest risk factor for the renal pelvis was smoking (RR = 11.0). Long-term regular use of phenacetin-containing analgesics was associated with increased risks of renal adenocarcinoma and cancer of the renal pelvis. Phenacetin use for 36 months or more had an RR of 8.0. There was some suggestion that cancer of the renal pelvis may be related to acetaminophen use. After adjustment for age, smoking, and phenacetin use, an RR of 6.1 was noted in female users for 36 months or more, but the numbers were small. In a recent carcinogenesis study, paracetamol induced liver cancer in 87% of the animals. These data suggest a future problem.

Dr. J. Ford described a case–control study in New South Wales. Phenacetin-containing analgesics and tobacco smoking increased the risk of renal pelvis cancer, with evidence of a synergistic effect of joint exposure. When the use of other analgesics was controlled for the consumption of phenacetin, paracetamol was not associated with a significant increased risk for cancer of any urologic site. The point estimates of RR for cancer of the renal pelvis were 0.9 in females and 2.1 in males. Risks for non-phenacetin analgesics were found with friend and screening clinic controls, but not with subsequent population controls. There is at present no other evidence of increased risk in Australia.

Dr. R. Ross described a case–control study in Los Angeles County in which the RR of renal pelvis cancer for smoking, the strongest risk factor, was 4.5. Heavy use of over-the-counter analgesics also increased risk. Any use of aspirin-containing analgesics for at least 30 days in any given year prior to diagnosis had an RR of 2.0.

Several research issues were raised: 1) Addictive use of phenacetin ceased only relatively recently, and it is likely that only a few persons with renal pelvis cancer have not used phenacetin. Because renal papillary necrosis precedes cancer by several years, case–control studies of newly diagnosed renal papillary necrosis were considered as one useful means we have of addressing the potential risk of non-phenacetin-containing analgesics, especially acetaminophen to which phenacetin is rapidly metabolized. 2) We need to determine whether the renal parenchyma or bladder is susceptible to analgesic-induced cancer.

Oral Cancer Investigation

The theme was how field and laboratory studies of oral cancer might contribute to our understanding of mechanisms of carcinogenesis. The focus was on chewing of betel in Asia and Melanesia and on "snuff dipping" in the southern U.S.

Betel is chewed by some 20% of the world population. Quids wrapped in the leaf of the betel pepper vine are chewed in Asia and contain areca nut, lime (which releases the alkaloid arecoline with pharmacologic effects similar to nicotine), and usually (but not always) tobacco and other additives. Unwrapped quids are chewed in Melanesia, and the constituents, which never include tobacco, are placed separately in the mouth. Evidence from Asia indicates that betel chewing is associated with oral cancer, but the contribution of the individual ingredients and possible synergistic effects of smoking and alcoholic beverages and the possible modifying effects of vitamin A and beta-carotene require further investigation.

Dr. Takeshi Hirayama reviewed Asian studies which strongly support a causal association between betel chewing and oral cancer. Asian chewers of tobacco without the areca nut get cancer at the site of contact in the mouth.

Dr. W. Blot described a study in South Carolina in which snuff applied to the buccal mucosa is the major risk factor. Tobacco is a common exposure in users of snuff.

The etiology of oral cancer in chewers of betel without tobacco in Melanesia and parts of Asia is not understood. A pilot case-control study in the Solomon Islands suggests that lime may be a key factor. Lime is highly irritating, often eroding the mucosa and producing much heat on contact with saliva in the mouth. Although inconclusive due to small numbers, results of the Solomon Islands study indicate that quids without lime may have a lower risk.

Two research issues were raised: 1) Case-control studies with quantitative data on all putative risk factors and modifiers of risk are needed. They should have adequate power and be appropriately analyzed, including modern multivariate methods, so that the risks of different ingredients in betel quids and possible interactions with other exposures can be assessed. 2) Such epidemiologic field work needs to be complemented by laboratory investigations, including studies of betel chewers. Because of its accessibility, the oral cavity may provide excellent opportunities for one to study mechanisms of carcinogenesis. The need exists for further carcinogenicity studies of the ingredients of betel quids and also for studies of the saliva of chewers, with and without evidence of neoplasia. The micronucleus test on exfoliated buccal mucosal cells was seen as a valuable method for the short-term monitoring of possible measures to prevent oral neoplasia.

Passive Smoking and Lung Cancer

Authors from 4 published studies on passive smoking and lung cancer were present in the Workshop (P. Correa, T. Hirayama, L. Koo, and B. MacMahon). Although no results are yet available, other studies are near completion, and this important issue should be reassessed in 6 to 12 months.

Dr. T. Hirayama's review was based on his recent letter to *The Lancet*. In Japan, Greece, and Louisiana the nonsmoking wives of smokers have an increased risk of lung cancer. Studies of wives of heavy smokers have provided evidence of dose-response relationships with an RR of approximately 1.9 in a cohort study in Japan and over 3.0 in case-control studies in Greece and Louisiana.

Dr. L. Koo described a case-control study of women in Hong Kong that included many nonactive smoking cases of lung cancer. Lifetime histories were taken so that estimates (in total hours) could be made of passive exposure to tobacco smoke in the home and at work. Generally, passive smoking was not found to increase the risk for lung cancer among Hong Kong Chinese females. Among smokers, passive exposure from external sources did not add to their risk. Among those who never smoked no evidence, qualitative or quantitative, showed a difference in risk between patients and controls. Only among the ethnic group Danjia/Helao (former boat dwellers) was there evidence of an added risk from passive smoking, and this could have been due to dietary or other life-style factors.

The research issues which surfaced during the discussions included the following: 1) How can we define and quantify passive smoking? 2) Does passive smoking increase the risk for lung cancer in smokers and nonsmokers? 3) What are the possible interactions with other life-style factors such as diet? 4) Why do nonsmoking Asian women develop lung cancer?

New Evidence on Causation of Lung Cancer

Dr. R. Prentice reviewed data on cigarette smoking and radiation exposure in relation to cancer mortality in Hiroshima and Nagasaki. Cancer mortality among 40,498 Hiroshima and Nagasaki residents was examined in relation to cigarette smoking habits and estimated atomic bomb radiation exposure level. The RR models that are either multiplicative or additive in the 2 exposures were emphasized. Most analyses were directed toward all nonhematologic cancer, stomach cancer, lung cancer, or digestive tract cancer other than stomach cancer for which there were 1,725, 658, 281, and 338 deaths, respectively, in the follow-up period for this study. Persons heavily exposed to both cigarette smoke and radiation were found to have significantly lower cancer mortality than multiplicative RR models would suggest for nonhematologic cancer, stomach cancer, and digestive tract cancer other than that of the stomach. Surprisingly, the RR function appeared not only to be less than multiplicative for some of these cancer site categories but may also be slightly less than additive. The estimated lung cancer RR function was also less than multiplicative, but not significantly so. The number of deaths was sufficient to permit more detailed study of the mortality from nonhematologic cancers. The RR functions appeared to be consistent between males and females, though the paucity of heavy smokers among females limits the precision of this comparison. The less than multiplicative nature of the RR function mentioned above was particularly pronounced among persons who were less than 30 years old at the time of the radiation exposure. The RR function for these younger subjects depends strongly on levels of radiation and cigarette smoke exposure.

CANCER REGISTRATION

This Workshop on Cancer Registration dealt with three broad categories relating to cancer registry functions.

Administrative Policy and Registry Operations

Mr. F. Foster described the ideal confidentiality policy for registries as one which would optimize utilization of registry data for research requiring patient contact, yet provide adequate protection of privacy for those registered. In the following discussion, it became clear that the California Tumor Registry is in the minority in its operating policy regarding physician contact prior to patient contact. Whereas many central registries ask the treating physician's approval to solicit a patient's participation in a study, the California Tumor Registry recognizes that the decision to participate or not is exclusively the right of the individual, not the individual's physician. Likewise, the treating physician is not legally liable for any unfavorable patient experience resulting from the study when she/he has not provided an authorization. Thus the operating policy at the California Registry is to contact the treating physician as a patient advocate and request her/his advice regarding any medical contraindication to contacting the patient at that time.

The importance of making an effort for assured accuracy of collected data was discussed, and Dr. H. P. Lee described a program of data review and staff motivation that was highly successful.

Innovations In Registry Operations

Mr. R. Gallagher described the plans of the Cancer Control Agency of British Columbia to evaluate the technique of obtaining follow-up status on cancer patients entirely by record linkage with national mortality data. This technique of passive follow-up is expected to be much cheaper. It requires altering the method of calculating survival rates because all patients not found to be dead are considered alive, in contrast with the prevailing methods of calculation.

The use of population-based survival statistics was discussed in conjunction with the possible use of site-specific mortality/incidence ratios as an alternative prognosticator statistic. The latter could make use of the fact that most persons whose death certificates mention cancer have specific histologic data recorded in the tumor registry. Thus the mortality data in such a ratio could have a high degree of accuracy.

Dr. D. Parkin described a software package developed by the International Agency for Research on Cancer for operating a small or hospital-based tumor registry. The software is designed to operate on a microcomputer costing under $10,000 and can handle up to 15,000 patients. Considerable discussion followed regarding similar efforts elsewhere. This resulted in the recognition that registry software developments should be internationally coordinated so that compatibility is assured and duplication of effort is eliminated.

Research Uses of Registry Data

Dr. L. Olivares demonstrated the use of comparative statistics to identify unusual incidence rates which may have important etiologic clues. She illustrated the striking deficit of tumors of the central nervous system in children of Lima, Peru, and the extraordinarily high rate of Hodgkin's disease in children there. This latter lymphoma has doubled in incidence for male children in the last 10 years and also increased in female children, whereas the rates of all other lymphomas remained stable.

Dr. G. Stemmermann illustrated the importance of evaluating the histopathology of tumors undergoing incidence changes and offered 2 examples. 1) The increase in ovarian cancer seen in Hawaiian Japanese is entirely due to an increase in epithelial types of ovarian cancer. 2) The decrease in stomach cancer occurring in Japanese migrants to Hawaii is equal in the intestinal and diffuse histologic types. This latter finding suggests that both types are etiologically related and that the 2 histologic types represent different host responses to a common environmental agent or combination of agents.

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